EXHIBIT G

Opinions of Lewis A. Chodosh, M.D., Ph.D.

This report is offered pursuant to Rule 26 of the Federal Rules of Civil Procedure. Each of the opinions I have offered in this report is given to a reasonable degree of scientific and medical certainty, and is based on the methods and procedures of science, materials and literature I have reviewed in connection with this litigation, my knowledge of recognized medical and scientific principles, and methodology reasonably relied upon by members of my profession, as well as my education, training, knowledge, and experience.

My curriculum vitae is attached as Exhibit A to this report. During the previous 4 years, I have testified as an expert at 1 deposition, and I have not testified as an expert in any trials. My testimony list is attached as Exhibit C. A My fees charged in connection with this engagement are consistent with my normal practice for such work. My rate for reviewing materials, preparing reports, and deposition and trial testimony is $850 per hour.

A list of materials that I considered in rendering the opinions offered in this report is attached as Exhibit B. I reserve the right to supplement this list, as well as to amend and supplement the opinions expressed in this report. I also reserve the right to respond to and rebut all information provided in discovery, which I understand is ongoing, and any opinions offered by Plaintiffs' experts at their depositions or at trial.

Citations to specific reference material also are offered in this report, where I believe it necessary to cite a specific source; otherwise, my opinions are derived from a combination of reference sources, my own scientific and clinical experience, and general medical and scientific knowledge. This report is not intended to be an exhaustive recitation of all of my opinions.

Background and Qualifications

1. I am a physician and cancer researcher. I graduated summa cum laude, Phi Beta Kappa from Yale University in 1981 with Distinction in Molecular Biophysics and Biochemistry. In 1989, I simultaneously received my M.D. degree from Harvard Medical School, where I graduated magna cum laude, and my Ph.D. degree in Biochemistry from the Massachusetts Institute of Technology under the mentorship of Dr. Phillip Sharp, who received the 1993 Nobel Prize in Physiology or Medicine. Dr. Sharp won the Nobel Prize for his discovery that each of our genes is split into pieces in our genome and for his work determining how a messenger RNA corresponding to a complete gene is spliced together from these pieces.

2. After a residency in Internal Medicine at the Massachusetts General Hospital, I completed a clinical fellowship in Endocrinology at the Massachusetts General Hospital in 1992. I then performed a postdoctoral research fellowship in cancer genetics and developmental biology with the Chairman of the Department of Genetics at Harvard Medical School, Dr. Philip Leder. Dr. Leder is widely credited with deciphering the genetic code by which the DNA sequences that encode genes are translated into proteins via a messenger RNA intermediate. In addition, Dr. Leder received the 1987 Albert Lasker Basic Medical Research

Award for his discovery of one of the first oncogenes recognized to cause human cancer, and his determination of how that oncogene was activated by a chromosomal rearrangement. Dr. Leder went on to create the very first genetically engineered mouse model for human cancer in order to prove that this oncogene could cause cancer in a living organism.

3. During my training, I received a number of additional honors including the Emerson Tuttle Cup for Distinguished Academic Achievement from Yale University, the Leon Reznick Memorial Prize for Excellence in Research from Harvard Medical School, and appointment to the Medical Scientist Training Program at Harvard.

4. I began my independent scientific career as an assistant professor at the University of Pennsylvania in 1994. As a faculty member in the Perelman School of Medicine at the University of Pennsylvania, I have received a number of awards and honors, including the Charles E. Culpeper Foundation Scholarship in Medical Science (one of three such awards made nationally to young physician-scientist faculty), the AACR-Sidney Kimmel Cancer Symposium for Cancer Research Scholar Award, and selection as the inaugural recipient of the Perelman Professorship and Endowed Chair in Cancer Biology. In 2002, I was elected to the American Society for Clinical Investigation. Established in 1908, the ASCI is one of the nation's oldest and most respected medical honor societies and is comprised of physician-scientists elected "for their outstanding records of scholarly achievement in biomedical research". In 2008, I was elected to the Association of American Physicians. Founded in 1885, the AAP is an honorary society whose goals include "the pursuit of medical knowledge, and the advancement through experimentation and discovery of basic and clinical science and their application to clinical medicine". In 2017, I was elected to the National Academy of Medicine, which is a part of the National Academies of the United States that were established by an act of Congress and signed into law in 1863 by Abraham Lincoln. Election to the NAM is considered one of the highest professional honors in medicine and medical research.

5. As a physician-scientist, the majority of my time is spent leading a research laboratory of approximately twenty-five graduate students, undergraduate students, research technicians, physicians and postdoctoral fellows in a comprehensive research program aimed at understanding the fundamental mechanisms that cause cancer, including understanding why cancers arise and progress in patients. As a principal investigator of a laboratory and as a mentor, I teach graduate students and postdoctoral researchers in the laboratory how to function as rigorous, critical-thinking experimental scientists, including how to design appropriate laboratory experiments to answer important biological questions, how to interpret the resulting data, how to prepare results for peer-review and publication, and how to critically read the scientific literature.

6. In addition, as a professor at the University of Pennsylvania I teach medical students, graduate students and undergraduate students in the classroom about principles of cancer biology, cancer epidemiology, and cancer therapy. I also teach physicians about cancer biology.

7. As a principal investigator of a laboratory at the University of Pennsylvania, I have focused on understanding the causes of cancer and on using that information to devise better methods of cancer prevention and treatment for patients. I am especially interested in

understanding the natural history by which human cancers arise and progress to more advanced stages, including the process of metastasis and the development of therapeutic resistance.

8. My laboratory uses a broad array of *in vivo* and *in vitro* models to study genes and mechanisms that are involved in the development of cancer in the breast and other tissues, including those related to inherited and acquired mutations in tumor suppressor genes and oncogenes. The first several publications from my laboratory focused on the *BRCA1* and *BRCA2* tumor suppressor genes. These two genes are involved in the cellular response to DNA damage and play key roles in suppressing cancers of the breast, ovary, pancreas, and other tissues. inherited mutations in *BRCA1* and *BRCA2* are responsible for the majority of cases of familial breast and ovarian cancer. Subsequent studies from my laboratory over nearly three decades have focused on the roles played by a variety of oncogenes, tumor suppressor genes, signaling pathways and genomic alterations in the development and progression of human cancers.

9. Model systems employed in my laboratory include in vitro studies of human and rodent cells in culture, studies of tissues from human patients, studies of genetically engineered mouse and rat models of human cancer, and studies of cell and tissue samples from cancer patients in the clinic. Particular areas of interest include: the function of oncogenes and tumor suppressor genes in cancer, metastasis, tumor dormancy (in cases where that occurs) and tumor recurrence; developmental windows of susceptibility to cancer initiation; the role of signal transduction pathways in cancer; the mechanisms by which cancers escape therapy; the role of inflammation, immunity, angiogenesis and the tumor microenvironment in cancer development and progression; the mechanisms controlling adipocyte (fat cell) differentiation; the roles of tumor initiating cells (*i.e.*, "cancer stem cells") in cancer; the mechanisms of metabolic regulation in cancer development and progression and in normal tissue physiology; the use of genomics and computational approaches to understand genetic programs in organ development and carcinogenesis; the use of noninvasive imaging approaches to study tumor biology; and the development of new diagnostic tests to address unmet needs in clinical oncology. In pursuit of these goals, my laboratory has developed several novel genetically engineered animal models for cancer, as well as a number of innovative approaches for analyzing large genomic data sets, imaging cancers, and identifying ultra-rare cancer cells that remain in some patients' bodies after they complete treatment. My laboratory is also integrally involved in the design and execution of clinical trials for cancer patients, including the analysis of clinical samples from patients enrolled in clinical trials investigating new treatments for cancer.

10. I currently serve as Perelman Professor and Chairman of the Department of Cancer Biology at the Perelman School of Medicine at the University of Pennsylvania, and I am a Professor with Tenure in the Department of Cancer Biology and in the Department of Medicine in the Division of Endocrinology, Diabetes and Metabolism. I also serve as Associate Director for Basic Science in the Abramson Cancer Center at the University of Pennsylvania, one of 51 National Cancer Institute-designated Comprehensive Cancer Centers in the United States, a designation that fewer than 4% of cancer centers in the Unites States receive. I have served as Director of Cancer Genetics, and now serve as Director of Tumor Biology, in the Abramson

Family Cancer Research Institute. I also co-founded and serve as co-Director of the 2-PREVENT Translational Center of Excellence at the Abramson Cancer Center, which is a multidisciplinary center aimed at preventing deaths from breast cancer recurrence in patients through novel clinical trials based upon scientific discoveries in the laboratory. Through these roles I contribute to, and help oversee the research programs of, more than 100 faculty members at the University of Pennsylvania who are focused on understanding the causes of human cancers, and the mechanisms that underlie their aggressive behavior and response to treatment.

11. In addition, I currently serve as a member of the scientific advisory board for the Dana-Farber/Harvard Cancer Center at Harvard Medical School, and I served for more than 15 years as a member of the scientific advisory board for the Harvard Nurses' Health Studies I and II. I have served as Principle Investigator for a Department of Defense Breast Cancer Center of Excellence, and for 10 years I served as Principal Investigator for one of the sites of the National Cancer Institute's Mouse Models for Human Cancers Consortium. I am Editor-in-Chief of the scientific journal *Breast Cancer Research*, and I have served as a Senior Editor of *Cancer Research* and on the editorial boards of *Cancer Biology and Treatment* and the *Journal of Mammary Biology and Neoplasia*. I also regularly serve as a peer reviewer for numerous journals, including *Nature*, *Science*, *Cell*, *Nature Medicine*, *Cancer Cell*, *Science Translational Medicine* and many others.

12. In my capacity as Principal Investigator, I have been awarded more than $60 million in extramural grants to support research in my laboratory, primarily from the National Cancer Institute, as well as from the Department of Defense and a variety of charitable foundations focused on supporting cancer research. I am also an Attending Staff Physician in good standing at the Hospital of the University of Pennsylvania and I am licensed to practice medicine in the states of Pennsylvania and Massachusetts. A more complete statement of my education, background, publications, and other work in the fields of cancer, molecular biology and developmental biology is contained in my CV that accompanies this report.

13. I maintain an office and my laboratory at 614 Biomedical Research Building II/III, 421 Curie Boulevard, Philadelphia, Pennsylvania.

14. The following opinions are based on my education, training, research, experience, knowledge of the literature, and information available to me at this time, and are based on a reasonable degree of medical and scientific probability and/or medical and scientific certainty. These opinions are offered to address issues related to general causation in this litigation. I may amend or supplement these opinions should any additional information be provided to me or if I learn of additional scientific literature that is relevant to this case. I may also amend or supplement this report in order to offer opinions on specific causation, or to rebut or respond to claims made by Plaintiffs' experts. I may use medical records, graphics or other materials to illustrate my opinions.

15. In addition to the current litigation that is the focus of this report, I have served as a consultant to the Department of Justice in a matter relating to vaccines and cancer. I have also participated in litigation as an expert witness and consultant in the matter of Hormone Replacement Therapy and breast cancer, in the matter of Actos and bladder cancer, in the

matter of talc and ovarian cancer, and in matters relating to asbestos exposure and mesothelioma in patients with inherited mutations in tumor suppressor genes. My rates for consultation in this matter are $850 per hour for testimony and all other work.

Overview

This report will address:

A. Background on human cancer causation

B. Evaluation of the claim that the presence of NDMA and/or NDEA in valsartan products is carcinogenic

C. Response to Plaintiffs' claims

Summary

A. Background: Human Cancer Causation

Cancer is a genetic disease caused by the accumulation of mutations in critical regulatory genes within the same cell

16. A tumor (or neoplasm) is an abnormal collection of cells that may be either benign or malignant. In benign tumors, abnormal cells remain clustered together and do not invade surrounding tissues. Malignant tumors, which are also referred to as cancers, do invade surrounding tissues and frequently metastasize to distant sites in the body.

17. Cancer is a disease in which abnormal cells bearing mutations (*i.e.*, errors in the DNA sequence of gene) divide in an uncontrolled manner and are able to invade other tissues in the body. DNA mutations may be inherited or acquired after birth.

18. There are well over 100 different types of cancer in humans, with many of these being subclassified into multiple subtypes. Despite this diversity, human cancers that arise in different tissues share many common properties.[1,2] Thus, the word "cancer" refers to a collection of distinct diseases that share a set of cardinal features. Cancers are sometimes referred to by clinicians as "solid" or "liquid". Solid tumors include carcinomas, sarcomas and cancers of the nervous system, whereas liquid tumors principally consist of leukemias and lymphomas.

19. Carcinomas are solid cancers that arise from epithelial cells, which are cells that line the organs of our bodies, such as the lung, breast, ovary, uterus, fallopian tube, prostate, bladder, oral cavity, esophagus, stomach, liver, pancreas, small intestine, and colon. Carcinomas represent approximately 85% of all human cancers and are far more common

than other types of cancer, such as leukemias, lymphomas, sarcomas, mesotheliomas, or cancers of the nervous system.

20. Cancer is frequently referred to in the scientific and medical literature as being a genetic disease. This refers to the fact that the process by which normal cells become cancerous entails the accumulation of genetic mutations in critical genes within the DNA of a single cell. Mutations can consist of point mutations (*i.e.*, single nucleotide changes), small insertions and deletions (*i.e.*, "INDELs"), copy number changes (*e.g.*, amplifications or deletions), gain or loss of all or parts of chromosomes, chromosomal translocations, or aneuploidy (abnormal numbers of chromosomes). Mutations may be either inherited (*e.g.*, *BRCA1*, *BRCA2*, *TP53*, *RB*, etc.), in which case they are present in every cell of the body, or acquired "somatically" after birth in an individual cell or cells as a consequence of normal cellular function and aging, or exposure to mutagenic agents.

21. Inherited mutations are often referred to as "germline" mutations, because they are present in either the sperm or egg (which are classified as "germ" cells) that gives rise to the fertilized egg. Since the fertilized egg represents the ancestral cell that gives rise to every cell of the resulting newborn child, any "germline" mutation will be present at birth in every one of a child's cells. Because a newborn child is made up of 1-2 trillion cells, a child with an inherited mutation begins its life with more than 1 trillion mutations.

22. Conceptually, the development of a cancer from a single, normal cell of origin to a cancer that can be detected clinically can be thought of as occurring in two stages. First, mutations in critical regulatory genes must accumulate within the same cell in a sufficient number, and in an appropriate combination, to generate the first (or ancestral) cancer cell. For cancers in adults, this process is believed to take many years, in most cases several decades.[3,4] Second, this initial ancestral cancer cell must subsequently expand in number to reach a clinically detectable size, which occurs via an imbalance between cell proliferation (also referred to as cell division) and cell death (also referred to as apoptosis or necrosis). This gradual expansion in cell number results in the accumulation of enough cells to reach a size that can be clinically detected, whether by medical imaging or by palpation, which is typically greater than 1 billion cancer cells. This net expansion of cancer cells is believed to occur over a period of years, typically a decade or more.[3,5] Importantly, the imbalance in cell proliferation and cell death that results in the net expansion of cancer cell number (also referred to as tumor growth) is typically driven by the same mutations that led to the development of the first cancer cell.

23. The behavior of normal cells in our bodies is tightly regulated, particularly with respect to whether (and when) a cell proliferates, whether (and when) a cell dies, and whether (and when) an undifferentiated cell such as a stem cell differentiates into a mature cell. In essence, the behavior of normal cells is controlled by signals emanating from the community of cells in the body, as well as the immediate environment of the cell, to ensure that all cells function in a coordinated manner in the organism as a whole. In addition, normal cells have a wide variety of safeguard mechanisms that allow them to repair DNA damage that they may sustain in the course of their everyday 'life', so that these do not result in mutations[3]. Additional safeguard

mechanisms allow damaged cells to initiate a 'self-destruct' program (termed programmed cell death or apoptosis) to destroy themselves if for some reason they are unable to repair DNA damage they have sustained. These, along with many other systems operating in cells and in the body, function as safety mechanisms that help prevent the development of cancer.

24. The essence of cancer is that mutations in critical growth control genes within the cancer cell generate all of the signals that the cancer cell requires in order to form a tumor. That is, the signals that are required for the survival, growth and proliferation of normal cells in our bodies typically originate outside the cell (*i.e.*, from the cells that surround it and from the bloodstream in the form of growth factors, hormones, etc.), and these signals are tightly regulated. In contrast, the signals that are required for the survival, growth and proliferation of cancer cells principally originate inside the cancer cell as a consequence of mutations in critical regulatory genes. These mutations result in the constitutive activation or inactivation of regulatory genes, which in turn drive uncontrolled cellular proliferation and cell survival, and abrogate normal differentiation pathways.

25. Importantly, the human body contains trillions of cells, the cells in our bodies undergo approximately 10^{16} cell divisions in our lifetimes (that is, 10 quadrillion – or 10 million, billion cell divisions) and every gene in our genome is estimated to undergo mutation 10^{10} (10 billion) times in our lifetimes, simply as a consequence of the normal function of the cells that make up our bodies.[3,6] This alone indicates that a single mutation cannot be enough to cause cancer in humans.

26. When one considers the enormous number of cells in our bodies in combination with our long lifespan, events important in causing cancer that may be quite rare when considering only a single cell in the body (*e.g.*, the accumulation of mutations in critical regulatory genes), may nevertheless be quite likely to occur in at least one cell in the body over the course of a lifetime.

27. The process by which a normal cell is transformed into a cancer cell is generally believed to require at least six different genetic mutations in critical genes ("cause"). Each of these mutations generally confers a new property or "hallmark" of cancer on the once-normal cell, such as: (1) self-sufficiency in growth signals; (2) insensitivity to anti-growth signals; (3) the ability to evade apoptosis (or programmed cell death); (4) the ability to induce the formation of new blood vessels; (5) the ability to proliferate forever; and (6) the ability to invade tissues and spread to other parts of the body (*i.e.*, metastasis).[1,3]

Cancer is caused by mutations in oncogenes and tumor suppressor genes

28. Cancer is caused by the accumulation of mutations in multiple critical growth control genes. These genes fall into two general classes: oncogenes and tumor suppressor genes.

29. An oncogene is a gene that, when constitutively activated by mutation, acts to promote tumor development, typically by driving unregulated cell growth, proliferation and/or survival. Oncogenes are most commonly derived from their non-mutated cellular counterparts (proto-oncogenes) by mutations that occur in cells of the body (*i.e.*, somatic

cells) during a patient's lifetime. Proto-oncogenes typically regulate cell growth, proliferation and survival. There are dozens of established oncogenes, including RAS, MYC, NOTCH1, PIK3CA, HER2, c-MET, EGFR, BRAF, FGFR1, AKT and BCR-ABL.

30. When functioning appropriately, the proteins encoded by tumor suppressor genes act to prevent tumor formation, typically by relaying growth-inhibitory signals, sensing and repairing DNA damage, or inducing programmed cell death in response to cellular stresses or warning signals. When mutations inactivate tumor suppressor genes, tumor development is promoted. There are dozens of known tumor suppressor genes, including TP53, RB, BAP1, p16, BRCA1, BRCA2, APC, and PTEN. Mutations in tumor suppressor genes may occur in somatic cells during a patient's lifetime, or they may be inherited from one or both parents. Inherited mutations in tumor suppressor genes are responsible for causing a variety of different inherited cancers and cancer susceptibility syndromes, whereby rates of certain cancers or groups of cancers occur within an extended family tree at higher rates than would be expected by chance. Importantly, it is also often the case that patients inheriting known cancer-predisposing mutations in tumor suppressor genes do not have an obvious family history of cancer.

31. The net result of the accumulation of mutations in oncogenes and tumor suppressor genes within a cancer cell is, among other things, that that cancer cell can proliferate and survive in an autonomous and unregulated manner. That is, the unregulated growth of cancers is a consequence of mutational events that occur inside the cancer cell, and the autonomous behavior of cancers is a direct consequence of these mutations.

32. Over the past decade, the genomes (*i.e.*, DNA genetic code) of many different types of human solid cancers – including those of the breast, ovary, colon, lung, prostate, stomach, esophagus, pancreas, bladder, mesothelium and others – have been sequenced in order to identify mutations in oncogenes and tumor suppressor genes that occurred during cancer development[7]. These studies have revealed that overlapping, though distinct, sets of oncogenes and tumor suppressor genes are mutated within different types of human cancers. This indicates that alterations in similar molecular pathways underlie the development of human solid cancers arising in different organs. For example, mutations in the p53 pathway are commonly found in many different types of human cancer. Despite this similarity, however, the specific sets of oncogenes and tumor suppressor genes that are recurrently (*i.e.*, commonly) mutated in different types of cancer tend to be distinct from each other.

33. Just as there are multiple oncogenes and tumor suppressor genes that are mutated within each cancer, the growth of any particular cancer is influenced by many different oncogenic pathways and is rarely, if ever, dependent upon a single pathway. This is one of the reasons why treating cancer effectively is so challenging. In addition, since there are many oncogenes and many tumor suppressor genes, the number of potential combinations of mutations in oncogenes and tumor suppressor genes that can result in cancer is enormous, so much so that almost no two cancers contain precisely the same set of mutated oncogenes and tumor suppressor genes. When combined with the many genetic (and other) differences between individuals (no two people are identical), this heterogeneity underscores why no two

cancers are identical. Nevertheless, cancers have many properties that are shared, including many molecular features that are shared, particularly within the same type of cancer.

Mutations, gene expression changes, and epigenetic alterations

34. Substances and exposures that can cause cancer are referred to as carcinogens. Most known human carcinogens are mutagens. Genotoxic or mutagenic agents cause DNA damage that, if unrepaired and passed on to a daughter cell, results in mutations. Many known human carcinogens, such as x-rays, ultraviolet light, viruses that insert their DNA into their host's genome, and certain chemicals in cigarette smoke, are known to cause DNA damage that can result in mutations. Such carcinogens are therefore referred to either as "genotoxic carcinogens" or "mutagens".

35. Since mutations resulting from DNA damage can take a wide variety of forms, including single nucleotide changes, small insertions/deletions, and chromosomal amplifications, deletions, translocations and aneuploidy, a single type of test cannot detect all genotoxic agents. Consequently, prior to the development and implementation of the full battery of tests capable of sensitively detecting the many types of DNA damage that can lead to mutations, some agents that were known to cause cancer were not found to be mutagenic when tested using only a limited number of assays, such as the Ames test. As a result, some of these agents were referred to as "non-genotoxic carcinogens". However, with subsequent testing using a broader range of assays it became clear that many of these agents did, in fact, cause DNA damage. Accordingly, by using a battery of tests capable of detecting the different types of mutations that can occur in cells, it is clear that many so-called "non-genotoxic carcinogens" actually do induce mutations in genes and/or chromosomes and therefore are, in fact, genotoxic. Thus, referring to an agent as a "non-genotoxic carcinogen" in no way implies that that agent does not cause mutations. Notably, valsartan has been tested using a battery of assays that cover the full spectrum of mutation types that can occur in cells, and has been found to be non-genotoxic, non-mutagenic and non-carcinogenic.[8]

36. Gene "expression" refers to the process by which the DNA encoding a gene, which is composed of a linear chain of deoxynucleotides, is "transcribed" to yield a messenger RNA (mRNA), which is composed of a linear chain of ribonucleotides that mirrors that of the gene. This mRNA is then "translated" by ribosomes in the cell to yield a protein, which is composed of a linear chain of amino acids specified by the mRNA nucleotide sequence.

37. The expression of each of the ~20,000 genes within each of the ~30 trillion cells in our bodies is tightly regulated in response to a variety of conditions inside the cell as well as external factors in a cell's local environment. This results in the transient up-regulation and down-regulation of the expression of a wide variety of genes and a wide variety of signaling pathways that relay messages within and between cells. These transient, tightly regulated changes in gene expression and activity are essential for the proper function of our cells and for our bodies as a whole.

38. It would be a mistake to equate the transient regulation of genes and signaling pathways that is part and parcel of normal cellular physiology with the impact of mutations in

cancer associated genes that constitutively turn "on" the activity of oncogenes or turn "off" the activity of tumor suppressor genes. Regulated changes in gene expression that occur during the normal cellular response to internal and external stimuli are transient, tightly regulated and required for our survival. In contrast, mutations that constitutively activate oncogenes or inactivate tumor suppressors result in the loss of regulation of those proteins and the pathways in which they play a role. It is this lack of regulation that results in the uncontrolled survival, growth, and proliferation signals characteristic of cancer cells.

39. Gene expression can also be regulated by epigenetic changes in cells. Epigenetic changes in gene expression are heritable (from one cell generation to the next) and do not involve alterations (*i.e.*, mutations) in the DNA nucleotide sequence of the genome. Rather, epigenetic changes typically result either from a variety of post-translational modifications of histone proteins that package DNA (*e.g.*, lysine/arginine methylation, lysine acetylation, serine/threonine phosphorylation, etc.), or from DNA methylation, which principally occurs as 5-methylcytosine residues at CpG dinucleotide sites in the genome. Clusters of CpG sites, referred to as CpG "islands", occur throughout the genome, particularly in areas of the genome that encode genes or that regulate gene expression.

40. As with transient changes in gene expression, the epigenetic regulation of gene expression is a normal physiological process that is essential for the proper function of our cells and tissues. It would be a mistake to equate the epigenetic regulation of gene expression with the impact of mutations in cancer associated genes, such as oncogenes or tumor suppressor genes. However, like the normal counterparts of oncogenes or tumor suppressor genes, epigenetic regulators can also be mutated in human cancers and, in doing so, these mutant regulators can function as oncogenes or tumor suppressor genes.

41. It would also be a mistake to equate the type of DNA methylation that mediates epigenetic changes in gene expression (*i.e.*, methylation at position 5 of cytosine to generate 5-methylcytosine) with the types of DNA damage that are induced by endogenous or exogenous alkylating agents, which may alkylate DNA at a variety of sites (*e.g.*, O^6-methylguanine). For example, in contrast to the normal physiologic role played by 5-methylcytosine present in CpG dinucleotides, methylated bases such as O^6-methylguanine constitute forms of DNA damage that must be repaired prior to DNA replication in order to prevent the occurrence of mutations.

Cancer is a disease of aging and develops over many years

42. As articulated above, for human cancers that occur in adults the process by which the mutations required to transform a normal cell into a cancer cell accumulate is generally believed to take decades.[3] It is for this reason that cancers that occur in adults are generally considered a disease of aging. Aging, in turn, is believed to be principally responsible for the mutations that result in most adult cancers, since the normal daily operation of our cells involves the generation of DNA damage that can result in mutations. These normal cellular processes may be referred to as "endogenous" sources of mutation. Although some types of human cancer have also been linked to exposures to mutagenic agents in the environment (*i.e.*, "exogenous" sources of mutation), in medical practice it is generally difficult, and in many cases impossible, to distinguish which mutations in a particular patient's cancer were

caused by endogenous versus exogenous processes, with the notable exception of mutations that are inherited.

43. Consistent with the long period of time required for the development of human cancers, human cancers with a discernable cause are usually diagnosed years or decades after the inferred causal event, as has been documented for many types of human cancer, including cigarette smoking and lung cancer, asbestos and pleural mesothelioma, ionizing radiation (*i.e.*, x-rays) and many forms of cancer, and ultraviolet light and melanoma. Given the extended periods of time required for sporadic human cancers to develop, there is no reliable scientific method to precisely determine when the first cancer cell arose in an individual patient. It is also generally not known when the first mutation occurred in the cell that ultimately developed into the first cancer cell. However, one exception to this is when a patient inherits a mutation in a critical cancer-related gene from one of their parents, every one of the trillions of cells in that person's body is known to contain a cancer-causing mutation at birth. Another important caveat is that while it is not possible to precisely determine when the first cancer cell arose in an individual patient, it is possible to reasonably estimate the minimum time periods and average time periods that are required for the development of cancers.

44. Perhaps the clearest manifestation of cancer in adults being a disease of aging is the observation that a patient's risk of being diagnosed with cancer increases exponentially with age. Observed rates for most adult cancers are relatively low for individuals in their 30s and 40s. Cancer rates begin to accelerate rapidly as patients age into their 50s, 60s and 70s. Furthermore, the magnitude of the exponential increase in cancer incidence as a function of age strongly suggests that multiple (*i.e.*, six or more) infrequent events (*i.e.*, mutations) must occur in specific, critical regulatory genes within the same cell in order to generate the first cancer cell. The requirement for multiple mutations to accumulate in critical regulatory genes within the same cell in order to create the first cancer cell is, in part, responsible for the long latency between exposure to an agent that causes cancer (like ionizing radiation) and clinical detection of the resulting cancer.

45. Another reason why human cancers take decades to develop is the net growth rate of cancer cells. There is a long period of time required for a normal cell to accumulate the multiple mutations required to generate the first cancer cell. It also takes a long period of time – typically years or even more than a decade – for that initial cancer cell to proliferate enough times to offset the high rates of cell death often seen in cancers and thereby enable an incipient tumor to accumulate a sufficient number of cancer cells to reach a clinically detectable size. As above, most human cancers are not detected until they contain billions of cancer cells.

46. For example, most breast cancers are believed to develop over a period of 30-50 years, as revealed by studies of women exposed to ionizing radiation (a known cause of breast cancer) during the atomic bomb blasts in Hiroshima and Nagasaki in 1945.[9-13] Remarkably, the great majority of the 'excess' breast cancers attributable to radiation exposure in survivors of the atomic bomb blasts occurred 30-50 years after exposure, which is in accordance with what we know about the natural history of breast cancer in human beings.

47. Similar to breast cancer, it has been estimated that the length of time required for the formation of a clinically detectable colon cancer is 30 – 50 years, and that each of the several rate-limiting events required for cancer formation may take, on average, 10 – 15 years or more.[3] Consistent with this, one of the key steps of colon cancer formation – the transition from polyp to invasive cancer – has been estimated by some to take as long as 17 years[3]. This represents the biological underpinning of the clinical guideline for performing screening colonoscopy in adults beginning at age 50 and, in the absence of positive findings (e.g., polyps), only repeating colonoscopy at 10-year intervals. Screening colonoscopy has been repeatedly proven to be an effective means to prevent the development of invasive colon cancers by removing pre-cancerous polyps. In light of that, its efficacy is predicated on the fact that human cancers, like colon cancers, have very long latencies on the order of decades. Put simply, if human cancers developed as rapidly as Plaintiffs' expert, Dr. Panigrahy, claims in this litigation, screening colonoscopy would never work. In fact, it does.

48. Similar to breast and colon cancer, the development of most common human cancers, including lung cancer, prostate cancer, ovarian cancer, pancreas cancer, stomach cancer, pleural mesothelioma, and many others, has been estimated to typically occur over 30-50 years, or longer[3]. This, in turn, is consistent with the exponential increase in the incidence of each of these cancers as a function of age, and with epidemiological data in those instances in which exposure to a known carcinogenic agent is involved.

49. Although the time course for the development of a human cancer is typically on the order of several decades, in some instances it is possible to detect an increase in cancer incidence in a shorter period of time. Accordingly, cohort studies with decades of follow-up can detect risks associated with the development of solid cancers over periods of time that are shorter than the median latency of those cancers. Returning to the example of breast cancer in survivors of the atomic bomb blasts at Hiroshima and Nagasaki, a discernable increase in breast cancer incidence attributable to ionizing radiation became evident in this population after approximately 11 years.[9-13] One model that would explain this observation is that these cancers could have resulted from x-ray-induced mutations in non-cancerous breast cells that had already accumulated mutations in multiple critical genes, such that the mutation induced by ionizing radiation was the 'final' mutation needed to create the first cancer cell. It is notable that, even in this scenario, these newly formed cancers did not reach a clinically detectable size for more than a decade. This is consistent with a variety of other observations indicating that it may take on the order of a year for the net number of cancer cells in a human breast cancer to double in a typical patient.[5] Consequently, from the moment that first cancer cell is created, it still takes more than a decade to accumulate the 1 billion or more cancer cells that is required for that cancer to come to clinical detection.

50. When considering the decades-long latency of most human cancers, a natural question that arises is why do children develop cancer, and how they can do so in shorter periods of time than those alluded to above. A potential misconception would be to assume that the amount of time that is required for some types of solid cancers to develop in adults can be inferred from the amount of time that it takes for different types of solid cancers to develop in children. It cannot. The fact that children sometimes develop cancer indicates that those particular types

of cancer can develop over a period of less than 10-15 years. However, there are several important differences between pediatric cancers and adult cancers that likely account for temporal differences in their incidence. First, as would be expected based on the concept that cancer is a disease of aging, cancer is a relatively uncommon disease in children compared to adults. Second, most types of solid cancer that do occur in children, such as medulloblastoma, neuroblastoma, Wilms tumor, retinoblastoma, osteosarcoma, and rhabdomyosarcoma, rarely, if ever, occur in adults. Conversely, it is extremely rare for children to be diagnosed with cancers of the lung, breast, prostate, colon, ovary, pancreas or bladder, which together represent the most common types of cancer that occur in adults. And for those types of cancer that do occur in both adults and children, their relatively frequency is markedly different. For example, leukemias and lymphomas account for more than 40% of childhood cancers, whereas these types of cancer account for less than 10% cancers in adults. These facts preclude direct inferences regarding the amount of time that it takes for adult solid cancers to develop to be drawn from the amount of time that it takes for different types of solid cancers to develop in children. Third, many childhood cancers are believed to result, at least in part, from inherited mutations in tumor suppressor genes, such as TP53 and RB, whose normal functions are to prevent cancer. Inherited mutational inactivation of these, or other, tumor suppressor genes in the fertilized egg that gives rise to a newborn child therefore dramatically increases that child's probability of developing cancer. This increased probability of developing cancer can be understood from the fact that such children are born with a critical mutation in every cell in their body and, as such, have trillions of mutations in their bodies when they are born. Fourth, pediatric cancers are generally believed to be less complex at the genetic level than solid cancers that occur in adults. That is, whereas solid cancers in adults are generally believed to require at least 6-8 mutations in critical genes within the same cell, pediatric cancers are believed to harbor mutations in perhaps one or two critical genes. Since many fewer mutations are believed to be required to cause the formation of pediatric cancers compared to adult cancers, such as bladder cancer, this process likely takes far less time in children. Taken together, these factors indicate that the pathogenesis of pediatric cancers follows rules that are very different from those governing adult cancers and precludes direct inferences regarding the amount of time that it takes for adult solid cancers to develop from being drawn based upon observations in children.

51. Another potential misconception would be to assume that the amount of time that it takes to develop a cancer in a human being can be inferred from the amount of time that it takes to develop a cancer in a mouse or a rat. It cannot. One way to envision this is that "time" is dramatically accelerated in mice and rats compared to human beings. To illustrate this fact, it is worth noting that mice live for two to three years (rather than the typical 70 to 80-year life span in humans), their gestational period is 18.5 days (rather than 280 days in humans), and they reach sexual maturity in 28 days (rather than the 13 years required in children). For these reasons and others, there is no scientifically reliable method for estimating the latency of a disease process in humans based upon the latency for a potentially related disease process in laboratory animals.

Mutations occur as a consequence of aging and are an inescapable consequence of the way our cells work

52. During many years of investigation, scientists have identified the cause of some of the mutations that cause cancers. For some types of cancer, these include agents in the environment, such as ionizing radiation, chemical carcinogens and certain viruses. For other types of cancer, however, environmental carcinogens appear unlikely to play a significant role.

53. Beyond these environmental exposures to carcinogens, however, it is clear that mutations occur frequently simply as a consequence of being alive. That is, our DNA is constantly being damaged and repaired as a consequence of the normal daily function of our cells.[3,14] For example, mitochondria – which can be thought of as tiny engines within our cells that use breakdown products of sugar (*i.e.*, glucose) as a fuel to generate energy – produce reactive oxygen species (ROS) as a byproduct of energy production. Although ROS play essential roles in normal cell physiology, ROS can also damage DNA within the cells in which they are produced, potentially leading to mutations. These causes of mutation are therefore considered to be unavoidable because they are "endogenous" (*i.e.*, due to factors within the body and/or within cells), rather than "exogenous" (*i.e.*, due to environmental factors outside of the body and/or outside of cells).

54. For these reasons, it is clear that developing cancer does not require exposure to an environmental carcinogen. Rather, mutations and cancer are frequently caused by endogenous 'exposures' that result from the normal functions of our cells. As an example of the inescapable nature of endogenous mutations, it is universally accepted that laboratory animals that are housed under extremely clean conditions without any exposures to environmental carcinogens for their entire lifetimes, still commonly develop spontaneous cancers over the course of their lifetime.

55. The fact that endogenous DNA damage occurs as a consequence of normal cell function likely explains – at least in part – why most adult solid cancers are a disease of aging.[3] Mutations that occur as a consequence of aging are almost certainly sufficient to cause human cancers, even in the absence of exposure to mutagenic agents in the environment. Indeed, current scientific evidence suggests that, for many cancers, molecular processes that normally occur within cells make a far greater contribution to the number of mutations that occur in those cells than do mutagenic agents in the environment to which people may be exposed. In his textbook, the "*Biology of Cancer*", Dr. Robert Weinberg highlights the astonishingly large number of DNA damaging events that occur in our cells every day, simply as a consequence of living:[3]

> *"12.5 Cell genomes are under constant attack from endogenous biochemical processes"* [Title of chapter section, p. 523]
>
> *"In recent decades, however, analytical techniques of greatly improved sensitivity have allowed researchers to detect altered bases and nucleotides in the DNA of normal cells that have not been exposed to exogenous mutagens. The results of these analyses have caused a profound shift in thinking about the origins of most of the mutant genes*

present in the genomes of human cells, because they have shown that endogenous biochemical processes usually make far greater contributions to genome mutation than do exogenous mutagens. Since mutagenic events, independent of their origin, are potentially carcinogenic, this has forced a rethinking of how many human cancers arise." (Pg. 523)

"By some estimates, as many as 10,000 purine bases are lost by depurination each day in a mammalian cell. (This amounts to more than 10^{17} chemically altered nucleotides generated each day in the human body!)" (Pg. 524-5)

"Taken together, the continuing hail of damage from oxidation, depurination, deamination, and methylation, which together may alter as many as 100,000 bases per cell genome each day, greatly exceeds the amount of damage created by exogenous mutagenic agents in most tissues." (Pg. 527)

If not inherited, the cause of the mutations that result in cancer are usually not known

56. Although some of the factors that can potentially give rise to mutations have been identified by scientists, either in the environment or inside cells as a consequence of aging, despite intensive investigation we do not know the precise factors within a cell that determine whether a somatic mutation will occur in any given context. Consequently, unless it is an inherited mutation known to cause cancer, we seldom know the cause of the mutations that gave rise to a particular patient's cancer. However, given the enormous amount of DNA damage that occurs in cells each day due to endogenous processes, it is most likely the case that the mutations that gave rise to a particular patient's cancer are simply a consequence of normal cell function and aging.

57. In this regard, even though it is known that human cancers are caused by the accumulation of mutations in multiple oncogenes and tumor suppressor genes, in the clinical setting physicians typically do not know the identity of the cancer-causing mutations in any given patient's cancer. Moreover, even if a somatic mutation in a particular oncogene or tumor suppressor gene is detected in a particular patient's cancer, what caused that mutation to occur is usually not known. For these reasons and others, even though we can determine with reasonable medical certainty that a particular cancer was caused by the oncogenic mutations present within it, we typically do not know the cause of those mutations and, in this sense, we typically cannot determine the cause of an individual person's cancer.

58. One exception to this occurs in the case of inherited mutations in genes, such as BRCA1, TP53, BAP1, and others. These inherited mutations have been demonstrated experimentally to cause cancer, are associated with enormous increases in cancer risks, and are present in the initial fertilized egg and, therefore, in every cell of the body. Since cancer is known to be caused by mutations in oncogenes and tumor suppressor genes, in those instances in which such mutations are identified in a patient's cancer, it is highly likely that those mutations contributed to the development of that cancer. This is particularly true in the case of inherited mutations in tumor suppressor genes, whose mutation may be associated with a massive increase in risk of

cancer that is comparable in magnitude to the increased risk of lung cancer associated with chronic cigarette smoking.

59. Put another way, in any individual cancer it is impossible to rule out a causal contribution of mutations in oncogenes or tumor suppressor genes to the development or growth of that cancer, and it is very likely that most of these mutations are due to endogenous processes. Indeed, pathogenic mutations in oncogenes and tumor suppressor genes identified in a particular cancer can logically be assumed to have causally contributed to the formation of that cancer.

60. In summary, there is no generally accepted scientific method for ruling out a substantial contribution of mutations in oncogenes and tumor suppressor genes accruing over time to the development of a cancer, cellular proliferation within a cancer, or tumorigenic effects such as cell survival, invasion, angiogenesis or metastasis. Moreover, the mutations that are present in any given cancer are often not determined in the clinical setting, and – even if they were – the causes of those mutations can only rarely ever be determined. For these reasons and others, medical science usually cannot determine the cause of an individual person's cancer.

Proliferation alone does not cause cancer

61. As noted above, in any given patient the first cancer cell forms by means of the stepwise accumulation of multiple mutations in key growth control genes within the same cell. Once formed, that first cancer cell grows into a clinically detectable cancer through the net proliferation and accumulation of cancer cells.

62. Cell proliferation is a normal physiological process that is ongoing and required for the health and maintenance of our tissues. In fact, without daily cell proliferation, we would die. While it is true that there must be some proliferation in order for cancer cells to accumulate, it is not true that if increased cell proliferation is present then the development of cancer is more likely. That is, current scientific thinking does not support the notion that the more rapid the rate of proliferation in a normal tissue, the greater the likelihood of that tissue developing cancer. For example, cell proliferation rates in bone marrow are amongst the highest in the human body, but cancers of bone marrow cells are quite rare compared to cancers of tissues with far lower proliferation rates, such as the lung and breast.

63. Processes that stimulate cell proliferation also often increase the rate of cell death. As such, since the growth of a subclinical cancer results from a net increase in the number of cancer cells, it is essential to account for changes in rates of cell death since an increase in the rate of cell death could result in a <u>decrease</u> in the number of cancer cells, even if proliferation continued – or even increased in rate – in that cancer.

64. A potential misconception is that cellular proliferation is, in and of itself, carcinogenic for the reason that increased rates of proliferation are associated with increased rates of replication of cellular DNA, which in turn may increase the chances that cells will accumulate genetic errors, or mutations. This hypothesis is unsupported by the body of scientific literature. At best, this supposition is speculative as proliferation-induced mutation is a hypothetical

consequence of proliferation, as opposed to a known consequence of proliferation in a given context.

65. Since the replication of DNA that accompanies cell proliferation formally has the potential to generate daughter cells harboring mutations in their DNA code, the body has developed safeguard mechanisms to prevent this from happening. These are predicated on the fact that DNA damage cannot give rise to a mutation unless the cell in which the DNA damage occurred replicates (*i.e.*, copies) its DNA and divides before that damage has been repaired. Since preserving the integrity of the DNA code within our cells is essential for life, our cells have developed numerous mechanisms for repairing DNA damage and thereby preventing the accumulation of cells bearing mutations. Such systems include base excision repair (BER), nucleotide excision repair (NER), homologous recombination (HR), mismatch repair (MMR), and others. Consequently, the same factors that stimulate cells to proliferate also turn on the expression of DNA damage sensing and repair proteins, such as BRCA1 and BRCA2, to ensure the faithful replication of DNA. As such, the induction of DNA repair proteins in proliferating cells is a normal cellular response that protects against mutations.

66. Beyond these DNA repair systems, additional cellular safety mechanisms exist that ensure that a cell has adequate time to repair DNA damage prior to replicating its genome in preparation for cell division. One such safety mechanism is mediated by the p53 tumor suppressor protein in which detection of the presence of DNA damage within a cell triggers that cell to halt its progression through the cell cycle, thereby giving the cell time to repair that DNA damage before it replicates its DNA or divides. In doing so, p53 prevents the occurrence of a mutation. Importantly, if for some reason the DNA damage in a cell cannot be repaired, p53 has the ability to trigger a "self-destruct" mechanism within that cell that forces it to undergo apoptosis (*i.e.*, programmed cell death), thereby leading to the elimination of that cell from the body. As a consequence, cells bearing DNA damage that cannot be repaired adequately prior to cell division can be eliminated. For this reason, a cell with DNA damage that is stimulated to proliferate may paradoxically be more likely to be eliminated through physiological safeguard mechanisms of this kind than a cell with DNA damage that is not stimulated to proliferate.

67. For the reasons enumerated above, one cannot simplistically link proliferation, mutation rates and cancer risk. Accordingly, it is factually incorrect to assume that a higher rate of cellular proliferation per se results in a greater mutation rate. While statements to this effect can be found in the scientific and medical literature, I am not aware of any published body of medical or scientific evidence demonstrating that a tissue that is proliferating at a higher rate accumulates mutations at a higher rate than that same tissue proliferating at a lower rate.

68. Indeed, a variety of evidence exists indicating that proliferation is not intrinsically linked to cancer risk, including the observations that: (1) proliferation rates in normal tissues are generally poorly correlated – if at all – with the incidence of cancers arising in those tissues; (2) an enormous amount of cellular proliferation is required for the development of a newborn child from a single fertilized egg, yet cancers in newborn children are exceptionally rare; (3) pregnancy has long been known to confer lifetime protection against the development of breast cancer, despite the fact that it is associated with high rates of cellular proliferation; and

(4) pregnancy protects against breast cancer even in women who already have breast cells with mutations, such as was the case with women exposed to ionizing radiation during the atomic bomb blasts at Hiroshima and Nagasaki.[9-13,15] For these and other reasons, proliferation per se cannot be equated with an increase in cancer risk.

Risk factors

69. Multiple risk factors have been elucidated for different human cancers, although the magnitude of many of these established risk factors is relatively small. Moreover, many patients who develop cancer have no apparent risk factors, other than age and/or gender. This likely reflects the fact that cancer is in many ways an unavoidable consequence of aging that has a random (or stochastic) component.

70. More importantly, it is essential to emphasize that there is a critical difference between a risk factor for a disease and a cause of that disease. A risk factor for cancer is merely a correlation between some factor and the development of cancer. The associations that risk factors represent cannot be equated with causality any more than having gray hair can be considered a cause of cancer – even though having gray hair is strongly associated with the development of cancer.

71. For a broad array of reasons, there is no accepted methodology, or reliable scientific or medical basis, to evaluate known and unknown risk factors in order to determine the cause of a particular patient's cancer, with the exception of inherited mutations in tumor suppressor genes that are known to cause cancer. First and foremost, risk factors cannot be considered causes; thus, 'ruling out' risk factors cannot logically be considered to be tantamount to ruling out potential causes of a patient's cancer. For example, obesity is an established risk factor for postmenopausal breast cancer, but no physician can reliably tell a patient that their breast cancer was caused by obesity. And even if risk factors were causes (they are not), they still could not explain causation for most patients. For example, risk factors for breast cancer include earlier age at menarche, later age at menopause, nulliparity, late age at first childbirth, lack of breastfeeding, obesity, mammographically dense breast tissue, family history of breast cancer, and others. However, each of these risk factors is associated with only a relatively small increase in risk and, in aggregate, a woman's risk factor profile is a notoriously poor predictor of her likelihood of developing breast cancer in her lifetime. Consistent with this, most women who develop breast cancer do not have known risk factors other than being female and growing older. For these reasons, a physician cannot ascertain the cause of a woman's breast cancer simply by ruling out known risk factors – because the list of potential causes for breast cancer do not explain why most women get breast cancer. Indeed, if the list of potential causes for breast cancer included being female and growing older, these would most often be the "causes" of cancer that remained after "ruling out" other risk factors.

72. Second, while cancer risk estimation may be reasonably accurate when applied to large populations, it is highly inaccurate when applied to individuals. Thus, even if risk factors were somehow able to establish causality across large populations, they would most likely be unable to do so in individuals.

73. Third, since most cancers likely arise from endogenous sources of mutations attributable to aging, aging (that is, being alive) itself is one of the most powerful risk factors for cancer and rarely, if ever, can be eliminated as a potential cause of adult human cancers.

74. A fourth reason why there is no accepted methodology, or reliable scientific or medical basis, to evaluate known and unknown risk factors in order to determine the cause of a particular patient's cancer is that, for many types of human cancer, medical science has only determined some of the potential causes or potential risk factors. Consequently, there is no reliable method to arrive at the "correct" cause simply by ruling out the incomplete set of causes (or risk factors) that do not appear to be operative in that patient.

75. The above notwithstanding, medical science has established that cancers are caused by the accumulation of mutations in critical genes within the same cell. It has also established that somatic mutations (those mutations that are not inherited in germ cells) typically occur as a consequence of the natural process of aging, and that such mutations occur even in the absence of any exposure to environmental or dietary mutagens. For this reason, aging-associated mutations must be considered as a potential cause of virtually every cancer that occurs in an adult.

76. To the extent that lists of potential causes of human cancers typically do not include mutations that occur as a consequence of the normal aging process, such lists are inherently incomplete. Since the current state of medical science does not permit the cause of each of the mutations that gave rise to a particular patient's cancer to be ascertained with medical certainty, the specific cause of a person's cancer typically cannot be determined by "ruling out" all other potential causes until a final suspected cause remains. Put another way, the final suspected "cause" of the cancer-causing mutations that most often remains for patients after ruling out known causes would be "idiopathic", which simply means that most people who develop cancer do so for reasons that cannot be determined with any reasonable degree of medical certainty.

77. For example, many would consider exposure to ionizing radiation, or inherited mutations in BRCA1 or BRCA2, to be known causes of human breast cancer. However, together these causes account for only a very small fraction of breast cancer cases. To attempt to ascertain the cause of a particular patient's breast cancer would, in the great majority of cases, rule out these two known causes, leaving only "idiopathic" as the suspected "cause". That is, the list of causes for human breast cancer is so grossly incomplete as to preclude the utility of differential diagnosis.

78. In this regard, if lists of causes of human cancer were truly comprehensive, they would include "aging-related mutations" and this would most often be the suspected cause that would remain after "ruling out" other possible causes. Moreover, since aging-related mutations generally cannot be ruled out as a cause of cancer, it is typically difficult, if not impossible, to eliminate aging as a cause of cancer. That is, when it comes to cancer, the fundamental premise upon which the utility of differential diagnosis rests – that all possible causes can either be ruled in or ruled out – only rarely can ever be met.

NDMA and NDEA: Background

79. *N*-Nitrosodimethylamine (NDMA, CAS 62-75-9) and *N*-Nitrosodiethylamine (NDEA, CAS 55-18-5) are dialkylnitrosamines, which are members of the *N*-nitroso class of compounds that contain both a nitroso (–N-N+O) functional group and an amine group (-NR_2, where R represents an alkyl group or H).[16,1718] For NDMA, R=CH_3, corresponding to a chemical formula of $C_2H_6N_2O$, a chemical structure of $(CH_3)_2$-N-N=O, and a molecular weight of 74.083.[16-18] For NDEA, R=CH_3CH_2, corresponding to a chemical formula of $C_4H_{10}N_2O$, a chemical structure of $(CH_3CH_2)_2$-N-N=O, and a molecular weight of 102.14. NDMA and NDEA are semivolatile oily liquids that are miscible in water and have boiling points of ~154°C and ~177°C, respectively.[16-18]

80. NDMA is found in the environment in air, water and soil, where it is formed by a chemical reaction between nitrosating agents (e.g., nitrite) and nitrosatable substrates (e.g., secondary amines), which are ubiquitously present in the environment.[16-18] For example, NDMA can be synthesized from amine compounds, nitrate and nitrite in the soil by bacteria. NDMA is rapidly degraded by sunlight-induced photolysis, but can be generated in the atmosphere at night by the reaction of dimethylamine (DMA) with nitrogen oxides.[16,17]

81. NDMA can also be generated as a by-product of industrial processes that employ amines, nitrate and/or nitrite, such as of rubber, pesticide and dye manufacturing, leather tanning, and food processing.[16-19] NDMA is most commonly formed when alkylamines react with nitrite, nitrous acid, nitrogen oxides. NDMA is present in exhaust fumes of diesel vehicles, may be generated by chemical reaction in sewage containing alkylamines and nitrate or nitrite, and is formed during treatment of drinking water as a consequence of chlorination processes.[16,17,20] NDMA is also present in some pesticides, either due to the manufacturing process or to formation under storage conditions.[16,17]

82. Human exposures to *N*-nitrosamines can be classified as either exogenous or endogenous. While NDMA and NDEA are but two members of the N-nitrosamine family, NDMA is by far the best studied. Exogenous exposures involve pre-formed NDMA, whereas endogenous exposures entail the synthesis of *N*-nitrosamines within the body. Significant sources of exogenous exposure to NDMA principally include indoor air (*i.e.*, environmental tobacco smoke), drinking water, food, beverage alcohol, tobacco, consumer products, and occupational exposures in certain industries.

83. Among exogenous exposures, tobacco generally entails the highest exposures.[17,19] In the absence of primary or secondary tobacco exposure, food is generally considered to be the principal determinant of exogenous exposure via intake of preformed NDMA, with beverage alcohol and drinking water accounting for progressively smaller percentages.[16,17,19]

84. Tobacco is a major source of exposure to high levels of nitrosamines, which are classified as volatile, non-volatile, and tobacco-specific N-nitrosamines.[21-25] NDMA is considered a semi-volatile nitrosamine. NDMA is formed both during the curing and fermentation process, as well as during combustion.[16,17,19] Nicotine can also serve as a precursor to NDMA formation,[21-23] and smokeless tobacco is also a significant source of NDMA

exposure. Environmental tobacco smoke (ETS) exposure (including mainstream smoke) has been estimated at 0.04-0.13 ug/kg/d due to ETS-contaminated indoor air, based on exposure to air concentrations that may be as high as 0.24 ug/m^3 for 21 hr/d.[17] Sidestream tobacco smoke concentrations of NDMA are on the order of 10-100-fold higher than mainstream smoke.[26] The ETS emission factor of NDMA for cigarettes can be greater than 500 ng/cigarette, although lower levels have also been reported.[26] Consequently, tobacco-related exposures may be 0.08-5.6 ug/d depending on level of cigarette smoking, for an upper range that may be as high as 2 mg per year, which is several times higher than likely dietary exposures to NDMA.[16,17,19]

85. Besides tobacco, food is estimated to be the major source of exogenous exposure to NDMA and other nitrosamines in humans.[16,17,25,27,28] Foods that tend to have the highest levels of NDMA and nitrosamines can be categorized into several groups. These include: (1) Foods preserved by nitrite and/or nitrate, such as cured meats (especially bacon) and cheeses; (2) Pickled and salt-preserved foods, particularly pickled vegetables in which bacterial reduction of nitrate to nitrite may occur; (3) Smoked meats and fish, due to nitrogen oxides in smoke; (4) Malt beverages, including beer and whiskey, principally due to drying of malt by hot flue gases; (5) Foods dried by combustion gases, such as dried milk products, malt, spices, due to nitrogen oxides in drying gases; and (6) Foods stored under humid conditions due to nitrosamine formation by contaminating bacteria.[16,17,19]

86. Precise quantification of dietary exposures to preformed NDMA and other nitrosamines in food is extremely difficult, in part because concentrations of NDMA and other nitrosamines in different foods change over time, can differ by geographic region, and are affected by numerous variables, including the method of preparation or preservation.[16,17,19] In addition, the types of foods consumed, as well as serving sizes, vary widely between individuals and data derived from self-reporting on dietary questionnaires are notoriously inaccurate.[29] It is also reasonable to note that dietary exposures relevant to cancer development likely occur decades prior to cancer diagnosis.

87. With these caveats in mind, reasonable estimates of daily dietary intake of NDMA can be made. For example, evaluating dietary NDMA levels (excluding beer or tobacco) from seven studies[30-36] yields an estimate of average daily intake of 0.164 ug/d, which would correspond to 0.0023 ug/kg/d for a 70 kg person, and a cumulative exposure of 4.19 mg over a 70-year lifetime. Liteplo et al.[17] reported "reasonable worst-case estimates" for daily intake of NDMA from food (excluding tobacco or beer/whiskey) for ages 20-59 years, which ranged from 0.0043 – 0.011 ug/kg/d. This would correspond to 0.30 – 0.77 ug/d, 110 – 281 ug/year, and 7.7 – 19.7 mg over a 70-year lifetime for a 70 kg person.

88. For reference, the FDA Acceptable Daily Intake (ADI) for NDMA is 96 ng/d, which corresponds to 35 ug per year and 2.45 mg over a 70-year lifetime (see below). Thus, daily dietary intake of NDMA, even excluding tobacco and beer, may often exceed the FDA ADI. Indeed, the estimates above for NDMA intake in food would range from 1.7 – 8.0-times higher than the FDA ADI. [17]

89. Liteplo et al.[17] estimated "reasonable worst-case estimates" of daily intake of NDMA in beer of 0.0009 ug/kg/d, which corresponds to 23 ug/year.

90. Although levels of nitrosamines in both food and beer have likely decreased in recent years relative to when many measurements of NDMA in foodstuffs were made, relatively few data exist defining the extent to which NDMA levels in different foods may have decreased.[37] In this regard, given that dietary exposures relevant to cancer development likely occur decades prior to diagnosis, it is pertinent that patients being treated with angiotensin II receptor blockers (ARBs), like valsartan, are generally older and therefore have had decades of lifetime exposure to nitrosamines from both exogenous sources (such as food, water, air, tobacco and beer) and from endogenous sources (see below). Accordingly, lifetime dietary exposures for such patients are likely to have included the higher levels of nitrosamines that were present in foods and malt beverages in the past.

91. Liteplo et al. reported "reasonable worst-case estimates" for daily intake of NDMA from food, water, and outdoor air (excluding tobacco or beer/whiskey) as being unlikely to exceed 0.008 ug/kg/d.[17] This would correspond to 0.56 ug/d, 204 ug/year, or 14.3 mg over the 70-year lifetime of a 70 kg person). The estimated daily intake of NDMA from food, air and water for ages 20-59 years ranged from 0.005 – 0.016 ug/kg/d.[17] This would correspond to 0.35 – 1.2 ug/d, 128 – 409 ug/year, and 8.95 – 28.6 mg over a 70-year lifetime for a 70 kg person. These estimates above for NDMA intake in food, water and air range from 3.6 – 11.7-times higher than the FDA ADI. Exposures would be higher for persons drinking beer and/or whiskey, and might be up to an order of magnitude higher for those with tobacco exposures.[17]

92. NDMA is also present in a number of consumer products, including personal care products and cosmetics such as shampoos, hair conditioners, bath and shower gels, and other products. Similarly, products containing rubber that contact the skin have NDMA, including latex gloves, baby bottle rubber nipples and pacifiers, ranging from 8.6 – 25 mg/kg NDMA.[17] Few data exist on the quantities of NDMA that might be absorbed via these routes of exposure.

93. Although NDMA has been more intensively studied than most other *N*-nitrosamines, NDMA is only one of the nitrosamines present in food and tobacco, or in industrial settings to which humans are exposed. Other nitrosamines, including NDEA, *N*-Nitrosodi-n-propylamine (NDPA), *N*-Nitrosodi-n-butylamine (NDBA), *N*-Nitrosomethylethylamine (NMEA) and *N*-Nitrosopyrrolidine (NYPR), have been reported to be present in foods, beverages, drugs, and tobacco smoke.[16,17,19] The average intake of volatile nitrosamines, including NDMA, is estimated at approximately 1 ug per day[38].

94. Since NDMA is a by-product of certain manufacturing processes, occupational exposures occur, most commonly via inhalation or dermal contact. This is the case in rubber and tire manufacturing, pesticide manufacturing, leather tanneries, dye manufacturing, fish meal production, rocket fuel industries, and others.[16,17]

95. Beyond exogenous exposures to NDMA from food, water, air, tobacco, beer, whiskey, and consumer products, endogenous exposures to NDMA are increasingly appreciated to be a major source – if not the major source – of exposure to NDMA and other nitrosamines.[30,39-42] Indeed, far from being synthetic molecules, NDMA and other nitrosamines are formed endogenously within the body, as a consequence of normal human physiology.[30,39-44] NDMA and other nitrosamines are formed endogenously from precursor compounds contained in

food, particularly secondary amines such as DMA in meats and fish, and nitrate and nitrite in vegetables. Indeed, reduction of nitrate by oral bacteria is considered to be the predominant source of nitrite in humans.[17,45] NDMA and other nitrosamines are formed endogenously in the gastrointestinal (GI) tract due to the metabolism of red meat in the presence of bacteria in the GI tract via a process dependent upon the presence of heme in red meat.[41,46-50] NDMA and other N-nitrosamines may also be formed by acid-catalyzed nitrosation, such as in the stomach, as well as by enzyme-catalyzed nitrosation.[51-55] Systemic nitrosation is driven by the family of enzymes known as nitric oxide (NO) synthases, which generate nitric oxide from the amino acid arginine.[56-58] Consistent with the endogenous formation of nitrosamines, including NDMA, O^6-methylguanine DNA adducts are observed in DNA in experimental animals that have not been exposed to environmental methylating agents, and in humans who are thought not to have been exposed to environmental methylating agents.[59-61]

96. Importantly, endogenous production of NDMA can be estimated to result in exposures that are approximately 1,875-fold higher than the highest estimated levels of exogenous exposure due to pre-formed NDMA in food, drinking water and air.[17] For example, Hrudey (2013)[30] utilized three different data types to estimate the amount of daily endogenous NDMA formation in humans. These estimates were: (a) 900 ug/d (12 ug/kg/d) based upon analysis of NDMA levels in blood samples considered in combination with blood clearance rates; (b) 1,360 ug/d (18 ug/kg/d) based upon levels of O^6-methylguanine in DNA from human blood, with estimates ranging as high as 17,000 ug/d; and (c) very wide estimates of endogenous NDMA formation based upon urinary excretion that encompassed the values estimated via the other two method. An average daily exposure to endogenously produced NDMA of 15 ug/kg/d, which represents the mean between estimation methods (a) and (b), would correspond to 1,050 ug/d for a 70 kg person, and 26.8 grams of NDMA over a 70-year lifetime. This level is approximately 1,875-times higher than the highest estimate of daily exposure to exogenous NDMA in food, drinking water and air[17], and nearly 11,000-times higher than the FDA ADI of 0.096 ug/d.

97. Using methodology analogous to Hrudey, Tannenbaum (1980)[62] estimated similar levels of endogenous NDMA production (670 ug/d). Vermeer (1998)[42] estimated that 174 ug/d of NDMA was produced endogenously in adult humans, based on data(Spiegelhalder 1982)[63] that 0.5% of NDMA formed is excreted in the urine. Further, Jakszyn (2006)[41] estimated that endogenous production of nitroso compounds (ENOCs) is 93-times greater than dietary exposure to NDMA, and these authors (and others) suggested that ENOC formation may account for observed associations between dietary red meat and processed meat intake and gastric cancer risk. Interestingly, while Jakszyn et al. found a significant increase in non-cardia cancer risk associated with endogenous exposure to NOCs, they did not find an association with pre-formed NDMA intake.[41] This finding is consistent with a model in which endogenous *N*-nitrosamine formation is of a substantially greater magnitude – and therefore more biologically important – than dietary intake of pre-formed nitrosamines.

98. The data above indicate that endogenous exposures to NDMA are likely to be at least two, and likely three, orders of magnitude higher than exposures to preformed NDMA in food, air and water combined. These data, and others, strongly suggest that the greatest human

exposure to NDMA, by far, occurs as a consequence of endogenous processes, not dietary intake.

NDMA and NDEA: Biological Effects in Animals

99. Ingested NDMA is absorbed rapidly. NDMA can also be absorbed through dermal contact, and by inhalation, although quantitative information related to the extent and timing of absorption is less clear.[16,17] NDMA and other nitrosamines in the circulation are cleared rapidly with both hepatic and non-hepatic clearance.[16-19] First-pass clearance within the liver following ingestion is a major contributor to clearance.[16,64,65] NDMA and its metabolites can be excreted in urine or exhaled as carbon dioxide. It has been estimated that less than 0.5% of NDMA is excreted in urine unchanged.[17,63]

100. Acute exposure to high doses of NDMA causes hepatotoxicity and liver failure in animals and in humans, as well as bleeding disorders, likely due at least in part to the hepatic first-pass clearance.[16] Exposure to lower doses of NDMA in animals result in elevated liver function tests.[16,17] These toxicities typically occur at doses higher than those associated with carcinogenesis. Liver toxicity has also been observed in humans in those rare instances in which acute exposure to NDMA has occurred at high doses.[16].

101. NDMA can be metabolized to formaldehyde and methylamine, and also to formaldehyde and monomethylnitrosamine, which can ultimately be converted to a methyldiazonium ion following activation by the cytochrome P450 system, particularly CYP2E1[16,17,19,66]. NDEA is also metabolized by CYP2E1 and can be converted to an ethyldiazonium ion.[67-69] These ions are electrophiles capable of reacting with macromolecules and can methylate (or ethylate, in the case of NDEA) proteins, RNA and DNA. The methyldiazonium ion has a very short half-life, such that the molecules with which it may interact are likely to be within the same cell – and certainly the same tissue – in which activation occurred.[17]

102. NDMA and NDEA are promutagens, which means that they are not capable of causing mutations until they have been metabolized (*i.e.*, chemically converted) into a mutagenic form. Thus, NDMA and NDEA have been shown to be mutagenic in vitro and in vivo in animals following metabolic conversion to a methyldiazonium/ethyldiazonium by virtue of their ability to alkylate DNA. For example, NDMA-mediated methylation of DNA can result in the generation of N^7-methylguanine, N^3-methyladenine, O^6-methylguanine, and O^4-methylthymine DNA adducts.[66,70-74] The most common DNA adduct formed as a consequence of NDMA is N^7-methylguanine, which represents approximately two-thirds of all adducts formed. In contrast, O^6-methylguanine has been estimated to represent only 7% of DNA adducts generated by NDMA.[71-73] Each of the above DNA adducts has different properties. For example, O^6-methylguanine is considered promutagenic, whereas N^7-methylguanine is not.[17] DNA adducts have been used as biomarkers of exposure to NDMA. However, since N^7-methylguanine is not mutagenic, it does not represent an accurate biomarker for NDMA-associated mutagenicity. Further, these DNA adduct biomarkers do not distinguish between endogenous versus exogenous exposures.[17]

103. As noted above NDMA is generated endogenously by both chemical and biological mechanisms at levels substantially higher than exogenous exposures to NDMA from food, air and water. Consequently, the DNA adducts that can result from exogenous exposure to NDMA are chemically indistinguishable from the DNA adducts that can result from endogenous exposure to NDMA (*i.e.*, in absence of exogenous NDMA exposure).[60,73,75] Moreover, levels of DNA adducts that result from endogenous NDMA exposures may be comparable to, or greater than, those associated with exogenous exposure.[60,73,75] For these reasons, while methylated DNA adducts represent a biomarker for DNA damage, these adducts to not distinguish DNA damage resulting from exogenous NDMA exposures from DNA damage that results from normal physiologic (*i.e.*, endogenous) processes.

104. Methylated DNA adducts that can form as a result of NDMA exposure are repaired over time by means of several endogenous error-free repair pathways.[76] O^6-methylguanine is repaired by O^6-methylguanine-DNA methyltransferase (MGMT), whereas N^7-methylguanine and N^3-methyladenine are repaired by N-alkyladenine-DNA glycosylase and the base excision repair (BER) pathway. The fact that these endogenous DNA repair systems exist – particularly MGMT – underscores the fact that DNA damage from alkylating agents such as NDMA is a normal physiological event.[77] Put another way, the enzyme MGMT, and the BER, NER and other DNA damage sensing and repair pathways, did not develop evolutionarily in order to repair DNA damage caused by man-made chemicals.

105. Of critical importance, DNA adducts that are successfully repaired by these endogenous DNA repair systems, or that lead to the death of the cell containing those DNA adducts, do not result in mutations.[38] Only those DNA adducts that are still present at the time of DNA replication have the potential to give rise to mutations. This reflects the critical distinction between DNA damage and mutation.

106. Given the ability of DNA repair systems to prevent mutations following exposure to DNA damaging agent (*e.g.*, genotoxic agent) such as NDMA, DNA repair is a critical determinant of dose-response effects for mutations induced by alkylating agents. That is, DNA adducts resulting from low-level exposures to agents like NDMA can be effectively and completely repaired, thereby avoiding the generation of mutations. In contrast, DNA adducts resulting from high-level NDMA exposures may lead to cell death (in which case mutations are not generated), or to mutations in those cells that replicate DNA containing unrepaired O^6-methylguanine adducts. Consequently, thresholds are observed for mutagenicity related to nitrosamine exposures such as NDMA, whereby DNA repair results in a non-linear dose-response for both mutagenesis and carcinogenesis for agents such as NDMA[78,79] and other mutagenic agents.[71,80-89] Indeed, as Guerard et al. stated: "For alkylating agents, DNA repair seems to be the pivotal mechanism in preventing genotoxicity at low doses, but other mechanisms are also involved such as MMR-mediated cell death to eliminate O^6MeG Harboring cells from the poplations."[81]. Consistent with this, Gollapudi *et al*. quantified in vivo mutation rates in the livers of rats that had been administered increasing doses of NDMA.[90] They found that the number of mutations was not elevated by treatment of rats with nine doses of NDMA at levels of 200 ug/kg/d or 600 ug/kg/d. Instead, a significant increase in mutations was not observed until doses of 2,000 ug/kg/d NDMA were administered. First, these data provide

additional evidence suggesting the existence of a threshold for NDMA-induced mutation in vivo. Second, it is worth noting that the lowest daily dose required to induce a detectable increase in mutations in rat liver, which is the most sensitive target tissue for NDMA-induced carcinogenesis in rats, was nearly 7,000 times higher than the highest dose of NDMA measured in any valsartan product.

107. For the above reasons, it would be scientifically incorrect to assume that each molecule of NDMA that is absorbed following exposure results in a mutation in DNA. First, not all NDMA is converted to a methyldiazonium ion. Second, since there is a very large number of molecules (*i.e.*, proteins, RNAs, DNA) in the cell with which a methyldiazonium ion can interact, the probability that a given methyldiazonium ion will methylate DNA, as opposed to another molecule, is considerably less than 1. Third, even for those ions that do methylate DNA, the probability of generating O^6-methylguanine, as opposed to a non-mutagenic DNA adduct such as N^7-methylguanine, is far less than 1. Fourth, even if an O^6-methylguanine adduct is formed, it may be repaired prior to DNA replication, or the cell in which it was generated may undergo DNA damage-induced apoptosis, such that no cellular mutation results. For these, and other, reasons, only a fraction of ingested NDMA molecules are likely to result in mutations, and there is almost certainly a threshold below which NDMA exposure does not result in mutations.

108. When administered at high doses, NDMA and NDEA reproducibly causes liver cancer in multiple species of laboratory animals and the liver appears to be the most sensitive site for tumorigenesis.[16,17,38,67,91-94] NDMA is also associated with a limited number of additional types of tumors in laboratory animals, predominantly those of the lung and kidney, with some variation observed across the wide range of animal species that have been tested, and occasional Leydig cell tumors of the testis.[16,17,38,91,92] NDEA is associated with both liver and esophageal cancer in rats.[67] At sufficient doses, NDMA-induced cancers consistently occur across a range of species, including rats, mice and hamsters, and by a variety of routes of exposure, including oral administration, inhalation and injection. However, while NDEA has been shown to cause liver tumors in non-human primates, NDMA has not.[38,95] Contrary to claims by Dr. Panigrahy that NDMA reproducibly causes cancers in a broad spectrum of tissues in experimental animals, most chronic oral carcinogenicity studies of rats, mice, and other experimental animals demonstrate carcinogenicity principally in the liver, with other consistent associations restricted to lung and kidney.[16,17,19,93]

109. The most extensive study for addressing carcinogenic effects of NDMA and NDEA in animals is generally considered to be those conducted by Peto (1991).[96,97] In this lifetime exposure experiment, 15 groups of 60 male and 60 female Coloworth-Wistar rats were provided increasing concentrations of NDMA or NDEA in drinking water ranging from 0.033-16.9 ppm, corresponding to daily intake estimates of approximately 0.001 – 0.697 mg/kg/d for males and 0.002-1.224 mg/kg/d for females. 120 males and 120 females served as controls. Groups of animals were sacrificed at 12 months and 18 months, with the remainder followed until death. Dose-related increases in tumor incidence were observed in the liver in both male and female rats, and included hepatocellular carcinoma and biliary cystadenoma. Dose-related increases in esophageal carcinoma and nasopharyngeal tumors were observed in the rats for

NDEA, but not NDMA. Background rates of liver tumors in rats were observed in the absence of treatment.

110. The lowest dose of NDMA observed to induce a significant increase in tumorigenesis, defined as that dose at which a 5% increase in tumorigenesis was observed (summarized/analyzed in Liteplo, 2002), was for biliary cystadenomas in female rats, which occurred at 0.034 mg/kg/d for biliary cystadenoma, and 0.082 mg/kg/d, hepatic carcinoma.[17,96,97] The corresponding doses for tumorigenesis in male rats were 0.035 mg/kg/d for biliary cystadenoma and 0.078 mg/kg/d for hepatic carcinoma.

111. Because of substantial background rate of hepatic tumors (approximately 8%) in rats followed for their lifetime, it was not possible to observe a dose-response effect of NDMA-induced tumorigenesis substantially below 0.034 mg/kg/d, which corresponds to an exposure in rats achieved by administering ~0.5 ppm NDMA in drinking water.[96,97] In contrast, due to the absence of background esophageal tumors, a no observed effect level for NDEA was evident at 0.264 ppm, corresponding to 0.0108 mg/kg/d for male rats and 0.019 mg/kg/d for female rats.[96,97] That is, there was no increased incidence of tumors in rats treated with doses of NDEA as high as 0.0108 mg/kg/d (0.264 ppm).

112. Importantly, animal studies of the carcinogenic effects of ingested NDMA consistently indicate that there are a limited number of tissues for which clear evidence exists for a dose-dependent tumorigenic effect in animals, and these include the liver, lung, kidney and, potentially, Leydig cell tumors of the testis.[16,17,93,94,96-98] Thus, oral ingestion of NDMA cannot reasonably be considered to be a universal carcinogen. Indeed, there are no carcinogens that I am aware of that cause cancer in all tissues.

NDMA and NDEA: Biological Effects in Humans

113. As noted above, exposures to NDMA and NDEA in humans can occur by ingestion, inhalation, or dermal contact.[16,17,19] Importantly, when exposures to NDMA and NDEA in human beings do occur, they are typically to a complex mixture of nitrosamines.[16,17,19] Consequently, biological effects of exogenous exposures to individual nitrosamines in humans cannot easily be distinguished from each other. Moreover, a corollary to this would be that cumulative exposures to nitrosamines in human beings are nearly always higher than those to NDMA alone.

114. Another factor complicating the inference of biological effects of nitrosamine exposures in human beings is the inherent difficulty in distinguishing exogenous exposures from the substantial levels of endogenous production of nitrosamines in humans, which may be two to three orders of magnitude higher than exogenous exposures, as discussed above.

115. Although NDMA and NDEA are known carcinogens in laboratory animals, they are not known carcinogens in humans. No cancers in humans have been conclusively demonstrated to result from exposure to NDMA or NDEA. There are no dose-response data from which to infer levels of exposure to NDMA or NDEA that might cause human cancers. Moreover, no regulatory agency has classified NDMA or NDEA as a known human carcinogen (see below).

116. Epidemiological studies of the effects of NDMA and NDEA principally consist of dietary studies and occupational exposure studies.[29] Each of these types of studies is subject to a variety of important limitations that preclude reliable interpretations regarding the potential carcinogenic effects of NDMA and NDEA in human populations.

117. For example, dietary epidemiology studies typically rely upon observational study designs based on self-reported dietary behavior. Beyond the fact that observational studies can never fully control for unrecognized bias and confounding, perhaps the major drawback to observational dietary studies is measurement error in dietary assessment.[29] First and foremost, the actual NDMA content in foods to which study subjects are exposed is rarely, if ever, measured in observational dietary studies. Rather, NDMA intake is inferred based on prior measurements of NDMA content in different foods, coupled with assessments of dietary intake that are typically based on self-reporting. The use of pre-existing data on NDMA content in food is itself associated with a variety of limitations and potential errors, including variation in NDMA levels even in the "same" food from different geographical regions, or grown, prepared or preserved in different ways.[29] Moreover, dietary assessments based on self-reporting are notoriously inaccurate (*e.g.*, do not correspond to actual intake), irrespective of whether the dietary assessment tool itself is "validated", insofar as validation of such tools generally refers to the presence of a correlation between dietary intake estimates based on the use of different assessment tools.[29] The complexity of human dietary patterns and practices is difficult to capture within a food questionnaire, self-reporting of foods consumed as well as portion sizes is subject to marked distortion and bias, and food histories queried many years after the meaningful exposures likely occurred (*i.e.*, with regard to cancer development) are intrinsically limited. For these reasons, and others, the actual dietary NDMA exposures of participants in observational dietary epidemiology studies is almost always unknown.

118. An additional critical drawback of dietary epidemiology studies is related to the complexity of foodstuffs. Foods typically contain thousands of chemical compounds, only a small minority of which may be measured. Even with respect to a single family of compounds, such as nitrosamines, multiple members of a family of molecules may be present in differing amounts in different foods. Consequently, there is a fundamental statistical limitation of interpreting correlations between the estimated dietary intake of a particular chemical (e.g., NDMA) and an outcome, because there are simply far more variables with respect to food composition than there are observations of outcomes. That is, there are not enough study participants, and not enough measures of the many different chemical compounds in the food they consumed (if any), to reliably determine the effect of one chemical compound. For example, an observed association of NDMA with a particular clinical outcome could result if estimated NDMA intake was merely a marker for another unknown or unmeasured exposure – even another nitrosamine. If the estimated NDMA dietary intake for a particular individual is high because they eat large amounts of bacon, there are obviously many other chemical compounds in bacon besides NDMA, and there are likely many things that differ between people who eat large amounts of bacon and those who do not, besides NDMA intake. Still more complex, if a person has a high estimated NDMA intake due to consumption of processed or grilled red meat, effects due to consumption of preformed NDMA cannot reasonably be separated from effects due to the endogenous generation of NDMA in the GI tract due to the

presence of heme in red meat, or to the generation of preformed carcinogens such as heterocyclic amines at high temperatures. These factors, and others, impair the reliability with which inferences can be drawn between the dietary consumption of a single constituent in foods and a particular clinical outcome, and these limitations are compounded further when the actual constituents consumed are not accurately measured, if at all.

119. In light of the above considerations it is evident that available dietary epidemiological studies focused on NDMA (a) do not actually measure NDMA intake in study participants; (b) do not measure the amounts of the thousands of other chemical constituents present in the food consumed by study participants; (c) cannot reliably distinguish potential effects of NDMA from the other constituents in food; (d) are unlikely to accurately measure food intake of study participants, irrespective of the chemical constituents contained within it; (e) do not measure food intake during the periods of time in which cancers actually form; (f) cannot rule out potential confounders and biases as explanations for any observed associations; and (g) cannot demonstrate cause and effect. For these reasons, and other, there is no medical or scientific basis by which existing dietary epidemiological studies of NDMA could reliably attribute any observed differences in cancers among study participants to NDMA.

120. These fundamental limitations of dietary epidemiology studies are exemplified by the many studies attempting to attribute cancer protective effects of food to specific vitamins and other chemical constituents in food. Numerous chemoprevention trials have been designed to test cancer prevention hypotheses based on epidemiological observations from dietary studies, coupled with apparently consistent evidence in animal and other experimental models, suggesting protective effects for a wide range of vitamins, nutrients and foods, including beta carotene, retinoids, selenium, vitamin C, vitamin D, vitamin E, antioxidants, and others. In the great majority of cases, randomized controlled trials have failed to find the predicted cancer-protective effect, and in some cases have demonstrated the opposite effect – an increase in cancer incidence or mortality.[99-107] These repeated failures to confirm cancer-related hypotheses based on dietary epidemiological studies highlight the marked limitations of observational dietary studies, and suggest a variety of possibilities, including that the dietary studies reached an incorrect result (*e.g.*, unrecognized confounding, etc.), that the effect observed was due to a different component or combination of components of food than the one measured, or that the component of food was simply a biomarker for an unrecognized protective factor or behavior.

121. Like dietary epidemiology studies, occupational studies related to the effects of NDMA exposure are also subject to important limitations that preclude reliable inferences regarding the effects of low-dose oral consumption of NDMA. These include the different route of exposure (inhalation vs. oral ingestion), higher levels of exposure, simultaneous exposure to multiple different potentially carcinogenic substances (*e.g.*, rubber dust, rubber fumes, NDMA, and other nitrosamines in rubber and tire manufacturing workers), and lack of information on important confounders (*e.g.*, smoking).

Assessments of Carcinogenicity by Regulatory Agencies

122. The U.S. Environmental Protection Agency (EPA) has classified NDMA as a "Group B2: Probable human carcinogen", which EPA defined under the 1986 guidelines as an agent for which "there is inadequate evidence that it can cause cancer in humans but at present it is far from conclusive".[18,98,108] This designation was for chronic inhalation.[108] Group B2 typically contains agents for which there is "sufficient" evidence from animal studies, but for which there is "inadequate evidence" or "no data" from epidemiologic studies.

123. The U.S. Department of Health and Humans Services has classified NDMA as "reasonably anticipated to be a human carcinogen".[109]

124. The American Conference of Governmental Industrial Hygienists (ACGIH) has classified carcinogenicity of NDMA as Group A3, which denotes a "confirmed animal carcinogen with unknown relevance to humans."[110] Specifically, the A3 designation indicates that "the agent is carcinogenic in experimental animals at a relatively high dose, by route(s) of administration, at site(s), or histologic type(s), or by mechanism(s) that may not be relevant to worker exposure. Available epidemiologic studies do not confirm an increased risk of cancer in exposed humans. Available evidence does not suggest that the agent is likely to cause cancer in humane except under uncommon or unlikely routes or levels of exposure."[110]

125. IARC (1978) has classified both NDMA and NDEA as Class 2A (*i.e.*, "probable") carcinogens based on sufficient evidence for carcinogenicity in experimental animals, similarities in its metabolism in human and rodent tissues, and inadequate evidence in humans.[93] Despite acknowledging the absence of epidemiological data, the IARC Working Group indicated that NDMA "should be regarded for practical purposes as if it were carcinogenic to humans." However, as articulated in their Monographs, IARC does not extrapolate exposure-response relationships beyond the available data, including from higher to lower exposures, or from experimental animals to humans.[111] In addition, IARC does not review quantitative risk characterizations developed by other health agencies.[111] Accordingly, IARC's determination of a carcinogenic hazard is essentially performed without regard to dose. That is, even if IARC designates a substance as a probable carcinogen based on high dose exposures in animals, it does not extrapolate this animal hazard to lower doses, or to human beings, and it therefore does not make a determination of whether an agent is likely to be carcinogenic to human beings at the low doses to which human beings might be exposed. In effect, IARC formulates an opinion on whether *any* dose of that agent might be carcinogenic, irrespective of whether it is a dose that might be encountered by human beings. In addition, IARC states that Monographs represent the views and expert opinions solely of the particular IARC Working Group assembled for that evaluation, and are not the view or opinions of the World Health Organization.

126. The European Medicines Agency (EMA) has classified NDMA as a "probable human carcinogen (a substance that could cause cancer) on the basis of animal studies."[112,113]

127. Health Canada (2018) has classified NDMA as a "probable human carcinogen" "based primarily on animal studies."[114]

128. Thus, assessments by each of the above agencies are based almost exclusively on evidence for carcinogenicity in experimental animals. In no case has an agency classified NDMA or NDEA as known human carcinogens, and no agency has cited human epidemiological evidence as supporting the designation of NDMA or NDEA as "probable" carcinogens.

NDMA, NDEA and Valsartan

129. Valsartan is an angiotensin II receptor blocker (ARB) used to treat hypertension and heart failure. It is manufactured in 40 mg, 80 mg, 160 mg and 320 mg dosages and is taken orally either daily or twice daily, with a maximum dosage of 320 mg.

130. In July 2018, the FDA announced the detection of NDMA in the active pharmaceutical ingredient (API) of certain valsartan products. In August 2018, the FDA announced the detection of NDEA in the API of certain valsartan products. Ultimately, multiple lots of generic valsartan were recalled in the U.S. due to the presence of NDMA and/or NDEA.

131. The central question at this stage of this litigation is whether exposure to NDMA and/or NDEA *at the doses to which Plaintiffs were potentially exposed via ingestion of valsartan, and within the time frame in which they were potentially exposed*, could have caused the types of cancer in human beings that are claimed in this litigation.

132. By using NDMA testing data from the FDA for valsartan products,[115] coupled with date ranges that particular valsartan products potentially containing NDMA were available on the U.S. market,[116] it is possible to calculate the theoretical maximum amounts of NDMA to which Plaintiffs could conceivably have been exposed from a particular product. For example, in calculating this theoretical 'highest exposure' to NDMA from Teva valsartan, I assumed that on any given day a hypothetical Plaintiff took the Teva valsartan product available on the market on that day that had the highest measured level of NDMA, starting conservatively from the date of FDA's approval of a process change by Teva's API manufacturer, September 29, 2014, until the date of Teva's final recall of valsartan products, November 27, 2018. To make this calculation even more conservative, I further assumed that on the day of product recall (*i.e.*, the last day that a Teva valsartan product was available on the U.S. market), a theoretical Plaintiff filled a 90-day prescription for the Teva valsartan product available on the U.S. market on that day, and continued to take that product for the entire 90-day duration of the prescription.

133. The maximum level of NDMA measured in any Teva valsartan product was 16.55 ug of NDMA in a 320 mg valsartan tablet. For a 70 kg person, this would correspond to a daily NDMA exposure of 0.000236 mg/kg/d. NDMA levels in multiple tested lots of Teva valsartan products were below the limits of detection. NDMA levels in other tested lots ranged from 6.94-16.55 ug/tablet. Thus, while 16.55 ug of NDMA represents an absolute upper bound on the amount of NDMA in a Teva valsartan product during the relevant time frame, it is extremely unlikely that any Plaintiff was exposed to these levels in every (or possibly in any) valsartan tablet that they ingested over the period in which they were taking valsartan products. Consequently, it is very likely that the average exposure to NDMA for any patient taking a valsartan product was substantially less than 16.55 ug/d.

134. The maximum theoretical duration of exposure to NDMA in a Teva valsartan product was 1611 days, based upon the first date that an NDMA-containing Teva valsartan product potentially containing NDMA became available on the U.S. market, 9/29/2014, until the date of recall on 11/27/2018, with an additional 90-day period added per assumption (d) below if a Plaintiff happened to fill a 90-day prescription for the Teva valsartan product available on the U.S. market on the day of recall. A Teva valsartan product containing 16.55 ug/tablet was available on the U.S. market from 9/29/2014-7/16/2018 (1387 days). However, Teva valsartan products available from 7/17/2018-11/27/2018 (134 days) were tested and determined by the FDA to have NDMA levels that were below the limits of detection.[115,116]

135. In light of the above, the maximum theoretical total NDMA exposure that conceivably could have occurred due to a Plaintiff taking an NDMA-containing Teva valsartan product can be estimated based on a series of assumptions, irrespective of however unlikely these assumptions may be. These conservative assumptions include: (a) the Plaintiff filled a prescription on the first day that a Teva valsartan product potentially containing NDMA was approved for sale in the U.S. under the process change; (b) that Plaintiff continued to take Teva valsartan products for the entire period from 9/29/2014-11/27/2018; (c) each and every Teva valsartan tablet that they received, and ingested, over the entire 4.4 year interval contained the highest measured dose of NDMA in any Teva valsartan product available on the U.S. market on that day; and (d) on the day of product recall they filled a 90-day prescription for the Teva valsartan product available on the U.S. market on that day, and continued to take that product for the entire 90-day duration of the prescription. If all of these assumptions were met, the maximum theoretical total NDMA exposure due to Teva valsartan product consumption would have be = (16.55 ug/tablet x 1387 days) + (0 ug/tablet x 134 days) = 22.96 mg NDMA. Again, for the reasons cited above, it is extremely unlikely that any Plaintiff was exposed to this amount of NDMA, because it is extremely unlikely that any Plaintiff fulfilled all four of the assumptions on which this theoretical 'highest exposure' calculation is based. Consequently, it is almost certainly the case that the cumulative exposure to NDMA for any Plaintiff taking a Teva valsartan product was substantially less than 22.96 mg.

136. In an analogous manner, it is possible to calculate the theoretical maximum total amount of NDMA to which Plaintiffs could conceivably have been exposed from *any* valsartan product produced by any combination of manufacturers. For this theoretical 'highest exposure' calculation, I assumed that on any given day a theoretical Plaintiff took the valsartan product available on the market on that day that had the highest measured level of NDMA, irrespective of manufacturer, from the first date that a valsartan product potentially containing NDMA was first approved for sale on the U.S. market, until the last recall date of 12/31/2018. In addition, I again used all four assumptions (a-d) above in order to calculate the theoretical maximum total amount of NDMA to which Plaintiffs could conceivably have been exposed.

137. Using NDMA testing data from the FDA for valsartan products,[115] coupled with date ranges that different valsartan products were approved for sale in the U.S.,[116] I identified the valsartan product with the highest level of NDMA that was available on the U.S. market for each day from 9/29/2014-12/31/2018. This permitted me to calculate the theoretical maximum exposure that conceivably could have occurred if a Plaintiff met all of the above

assumptions, a-d. This would correspond to a Plaintiff taking the following manufacturers' valsartan products for the following indicated time periods: 9/27/2014-2/8/2016 (Teva Pharmaceuticals, 16.55 ug/tab, 498 days); 2/9/2016-7/18/2018 (Prinston Pharmaceutical, 20.19 ug/tab, 891 days); and 7/19/2018-8/22/2018 (Torrent Pharmaceuticals, 11.53 ug/tab, 35 days). From 8/23-2018-12/31/2018, no valsartan product on the U.S. market contained NDMA above the limit of detection. This hypothetical scenario corresponds to a theoretical maximum total NDMA exposure of 26.64 mg over 1611 days. Again, it bears noting that it is extremely unlikely that any Plaintiff was exposed to this amount of NDMA, because it is extremely unlikely that any Plaintiff fulfilled all four of the assumptions on which this theoretical 'highest exposure' calculation is based. In particular, it is almost inconceivable that any Plaintiff happened to take the exact lot of valsartan product that contained the highest amount of NDMA every day during this 4.4-year period. Consequently, it is almost certainly the case that the cumulative exposure to NDMA for any Plaintiff taking any valsartan product was substantially less than 26.64 mg.

138. In precisely the same manner, by using NDEA testing data from the FDA for valsartan products,[115] coupled with date ranges that different manufactured lots of valsartan were available on the U.S. market,[116] it is possible to calculate the theoretical maximum amounts of NDEA to which Plaintiffs could conceivably have been exposed from a particular valsartan product. Again using Teva as an example, the maximum level of NDEA measured in any Teva valsartan product was 0.77 ug of NDEA in a 320 mg valsartan tablet. For a 70 kg person, this would correspond to a daily NDEA exposure of 0.000011 mg/kg/d. NDEA levels in multiple tested lots of Teva valsartan products were either below the limits of detection, or ranged from 0-0.03 ug/tablet. NDEA levels in other tested lots ranged from 0-0.77 ug/tablet. Thus, while 0.77 ug represents an upper bound on the amount of NDEA in a Teva valsartan product during the relevant time frame, it is nevertheless unlikely that any one person was exposed to these levels in every (or possibly in any) valsartan tablet that they ingested.

139. Applying the same assumptions used above for NDMA, the maximum theoretical duration of exposure to NDEA in a Teva valsartan product was 1611 days, based upon the first date that an NDEA-containing Teva valsartan product was approved for sale in the U.S., 9/29/2014, until the date of recall on 11/27/2018, with an additional 90 days added per assumption (d). A Teva valsartan product containing 0.77 ug/tablet was available on the U.S. market from 9/29/2014-7/16/2018 (1387 days).[115,116] From 7/17/2018-11/27/2018 (134 days) the Teva valsartan product with the highest level of NDEA was 0.03 ug/tablet. I then assumed that a Plaintiff filled a 90-day prescription on the day of product recall for this Teva valsartan product and continued to take that product for the entire 90-day duration of the prescription. If all of the above assumptions were met, however unlikely that might be, the maximum theoretical total NDEA exposure due to Teva valsartan product consumption would have be = (0.77 ug/tablet x 1387 days) + (0.03 ug/tablet x 134 days) + (0.03 ug/tablet x 90 days) = 1,075 ug NDEA. Again, for the reasons cited above, it is extremely unlikely that any Plaintiff was exposed to this amount of NDEA, because it is extremely unlikely that any Plaintiff fulfilled all four of the assumptions on which this theoretical 'highest exposure' calculation is based. Consequently, it is almost certainly the case that the cumulative exposure to NDEA for any Plaintiff taking a Teva valsartan product was substantially less than 1,075 ug.

140. In a manner analogous to the calculation performed for NDMA, I calculated the theoretical maximum total amount of NDEA to which Plaintiffs could conceivably have been exposed from *any* valsartan product produced by any combination of manufacturers. I assumed that on any given day a theoretical Plaintiff took the valsartan product available on the market on that day that had the highest measured level of NDEA, irrespective of manufacturer, from the first date that a valsartan product potentially containing NDEA was sold in the U.S., 9/21/2012, until the last date a valsartan product potentially containing NDEA was recalled, 12/31/2018. In addition, I again used all four assumptions (a-d) above in order to calculate the theoretical maximum total amount of NDEA to which Plaintiffs could conceivably have been exposed.

141. Using NDEA testing data from the FDA for valsartan products,[115] coupled with date ranges that different manufactured lots of valsartan were available on the U.S. market,[116] I identified the valsartan product with the highest level of NDEA that was available on the U.S. market for each day from 9/21/2012 – 12/31/2018. This permitted me to calculate the theoretical maximum exposure that conceivably could have occurred if a Plaintiff met all of the above assumptions, a-d. This would correspond to a Plaintiff taking the following manufacturers' valsartan products for the following indicated time periods: 9/21/2012-9/28/2014 (Mylan Pharmaceutical, 0.38 ug/tab, 738 days); 9/29/2014-12/31/2014 (Teva Pharmaceuticals, 0.77 ug/tab, 72 days); 1/1/2015-8/22/2018 (Torrent Pharmaceuticals, 1.31 ug/tab, 1330 days); 8/23/2018-12/4/2018 (Mylan Pharmaceutical, 0.38 ug/tab, 104 days), and 12/5/2018-12/31/2018 (Aurobindo Pharma, 0.19 ug/tab,27 days), plus 90 additional days for Aurobindo Pharma at 0.19 ug/tab. This corresponds to a theoretical maximum total NDMA exposure of 2,157 ug over 2,383 days. Again, it bears noting that it is extremely unlikely that any Plaintiff was exposed to this amount of NDEA, because it is extremely unlikely that any Plaintiff fulfilled all four of the assumptions on which this theoretical 'highest exposure' calculation is based. In particular, it is almost inconceivable that any Plaintiff happened to take the exact lot of valsartan product that contained the highest amount of NDEA every day during this 6.5-year period, even if they were taking a valsartan product for that entire period of time. Consequently, it is almost certainly the case that the cumulative exposure to NDEA for any Plaintiff taking any valsartan product was substantially less than 2,157 ug.

142. To my knowledge, the actual amounts of NDMA and/or NDEA to which individual Plaintiffs in this litigation may have been exposed has not been documented. Moreover, while it is theoretically possible to meet each of the four assumptions outlined above, it is nevertheless highly unlikely to have actually occurred for any given Plaintiff. Accordingly, the above estimates of maximum theoretical exposures to NDMA and NDEA are hypotheticals presented to provide a concrete, if extreme, upper bound for the purposes of evaluating theoretical risks in the context of other exogenous and endogenous exposures to NDMA and NDEA.

Regulatory Agencies: Risk Estimates

143. The U.S. Food and Drug Administration has set an Acceptable Daily Intake (ADI) of 96 ng/d for NDMA, and 26.5 ng/d for NDEA, for pharmaceutical products. These ADI values were

estimated by the FDA to result in <1 excess case of cancer per 100,000 people, if taken every day for 70 years. These ADI values for NDMA and NDEA are equivalent to exposures of 35 ug/year and 2.45 mg over a 70-year lifetime for NDMA, and 9.7 ug/year and 678 ug over a 70-year lifetime for NDEA.

144. In effect, these ADI values were derived by linear extrapolation from high oral doses of NDMA and NDEA in a lifetime exposure study that resulted in tumors in 50% of rats (Peto 1991),[96,97] to a far lower dose estimated to be associated with an increase of 1:100,000 cancers in humans over a 70-year lifetime. There are several important elements of this extrapolation. First, this estimation approach is derived from back extrapolation of animal studies, rather than human studies, since no human studies exist that demonstrate a cause and effect relationship between NDMA or NDEA exposure and the development of cancer. Second, these ADI values are based on linear low-dose extrapolation; namely, the assumption that the dose-response for NDMA and NDEA-induced carcinogenesis remains linear even at extremely low doses that are many orders of magnitude lower than what can possibly be measured, even in experimental animal models. Thus, there is no body of direct evidence to support the linear dose-response assumption for NDMA and NDEA at the extremely low doses to which patients could theoretically have been exposed. Further, as discussed below, there is direct evidence to the contrary suggesting that the linear low-dose assumption is unlikely to be true for NDMA and NDEA. Third, while it is understandable why the safety mandate of the FDA would lead it to err on the side of conservative risk estimates, it nevertheless bears noting that a 1:100,000 threshold for cancer development is extraordinarily conservative, particularly considering that the lifetime risk of being diagnosed with cancer is approximately 1 in 2, which constitutes a risk that is 50,000 times higher than FDA estimates of cancer risks attributable to lifetime exposure to NDMA at 96 ng/d or to NDEA at 26.5 ng/d. Indeed, the FDA has noted that "consuming up to 0.096 micrograms of NDMA of 0.0265 micrograms of NDEA per day is considered reasonably safe for human ingestion based on lifetime exposure."[115,117]

145. Based upon its evaluation of NDMA-containing valsartan products, the FDA estimated that the amount of NDMA contained in valsartan products might be associated with a theoretical excess lifetime cancer risk of 1:8,000 people if exposures occurred continuously at the maximum possible daily dose for a maximum duration of 4 years. Similarly, the FDA estimated that the amount of NDEA contained in valsartan products might be associated with a theoretical excess lifetime cancer risk of 1:18,000 people if exposures occurred continuously at the maximum possible daily dose for a maximum duration of 4 years.

146. The FDA also noted that "in reality, the vast majority of patients exposed to NDMA through [angiotensin II receptor blockers] ARBs received much smaller amounts of the impurity than this worst-case scenario, and, since not all ARBs are affected, it's very likely that a patient taking an ARB for four years would not have always received one of the affected products." Consequently, FDA indicated that while they had based their cancer risk estimates on the highest daily dose, "many people may have taken lower doses, and therefore, their risks would theoretically be less. FDA expects the actual cancer risk to most consumers to be lower than our estimate." Indeed, FDA characterized the cancer risks associated with valsartan containing NDMA and/or NDEA as "very low". In addition, the FDA also indicated that they "strongly

believe the risks, such as stroke, of abruptly discontinuing these important medicines far outweighs the low risk associated with continuing the medications with these impurities," and, on that basis, advised that "patients should continue taking their medicine until their pharmacist provides a replacement or their doctor provides an alternative treatment option – even if they learn that their ARB medicine is recalled."

147. Using similar risk estimation approaches, Health Canada estimated a maximum theoretical excess lifetime cancer risk of 1:11,600 due to consumption of NDMA-containing valsartan products, assuming an average level of NDMA of 60 ppm, a dosage of 320 mg valsartan, and exposure for 3 years, which corresponds to the longest time that NDMA and/or NDEA-containing valsartan products were on the Canadian market.[114] Health Canada also noted that "it is important to keep in mind that the actual health risk varies from person to person, and depends on factors including daily dose, how long the affected valsartan was taken, and the actual level of NDMA present in the finished product", that "we are all exposed to low levels of NDMA", that "to put these estimates into a broader context, nearly 1 in 2 Canadians is expected to develop cancer during their lifetime," and that NDMA "is not expected to cause harm when ingested in very low levels."

Theoretical maximum levels of NDMA exposure from valsartan products are orders of magnitude lower than levels of endogenous NDMA production

148. The highest conceivable total amounts of NDMA and/or NDEA to which Plaintiffs could possibly have been exposed due to ingestion of valsartan products are more than three orders of magnitude lower than the lowest dose associated with a detectable increase in cancer in rats, and are two to three orders of magnitude lower than estimates of endogenous NDMA production. When considering that, for the reasons cited above, the cumulative exposure to NDMA and/or NDEA for any patient taking a valsartan product was almost certainly substantially lower than the highest conceivable cumulative amount, the magnitude of the difference between a patient's cumulative exposure to NDMA and/or NDEA due to ingestion of valsartan products and the lowest dose of NDMA and/or NDEA associated with a detectable increase in cancer in rats is likely even greater.

149. As above, estimates of endogenous levels of daily NDMA production range from 174 ug/d (Vermeer 1998)[42] to 1,360 ug/d (Hrudey 2013),[30] and higher. In my opinion, the most thorough and systematic analysis was that of Hrudey, which estimated endogenous NDMA production using multiple distinct approaches at 900 ug/d (12 ug/kg/d) based upon analysis of NDMA levels in blood samples in combination with blood clearance rates, and 1,360 ug/d (18 ug/kg/d) based upon levels of O^6-methylguanine in DNA from human blood. Thus, the mean of these two estimation methods would yield an average daily exposure to endogenously produced NDMA of 15 ug/kg/d, which for a 70 kg person would correspond to a daily NDMA exposure of 1,050 ug/d, and a cumulative exposure of 26.8 grams (26,800 mg) of NDMA over a 70-year lifetime. This level of endogenous NDMA exposure is approximately 1,875-times higher than the highest estimate of NDMA daily dietary intake,(Liteplo, 2002)[17] and nearly 11,000-times higher than the FDA ADI of 0.096 ug/d.

150. Again using Teva as an example, and assuming a maximum theoretical daily exposure to NDMA from ingestion of Teva valsartan products of 16.55 ug, this amount of NDMA is 10.5-times lower than estimates of endogenous daily production of NDMA by Vermeer, and 64-times lower than the average estimate of endogenous daily NDMA production by Hrudey. Thus, even ignoring daily exogenous exposure to NDMA due to diet, the maximum theoretical amount of NDMA in Teva valsartan products to which a patient might have been exposed represents just 1.6% – 9.5% of the amount of NDMA that is estimated to be produced endogenously each day.

151. When considering maximum theoretical daily exposure to NDMA from ingestion of *any* valsartan product, which was 20.19 ug, this amount of NDMA is 8.6-times lower than estimates of endogenous daily production of NDMA by Vermeer, and 52-times lower than the average estimate of endogenous daily NDMA production by Hrudey. Thus, even ignoring daily exogenous exposure to NDMA due to diet, the maximum theoretical amount of NDMA in *any* valsartan product to which a patient might have been exposed represents just 1.9% – 11.6% of the amount of NDMA that is estimated to be produced endogenously each day.

152. When evaluating cancer risk associated with exposures to carcinogenic agents, total lifetime exposure is a more accurate measure of lifetime cancer risk than daily exposure. As above, the maximum theoretical total exposure to NDMA to which a Plaintiff could conceivable have been exposed due to ingesting Teva valsartan products was 22.96 mg, if and only if each and every Teva valsartan tablet that they ingested over the entire 1,610-day interval contained the highest measured dose of NDMA in any Teva valsartan product available on the U.S. market on that day. In contrast, estimates of cumulative lifetime endogenous NDMA production based on Hrudey correspond to 26.8 grams of NDMA over a 70-year lifetime. This level of NDMA exposure due to endogenous production is greater than 1,100-times higher than the maximum theoretical total exposure to NDMA due to ingestion of Teva valsartan products. Thus, the maximum theoretical cumulative exposure to NDMA from Teva valsartan products represents – at most – just 0.1% of estimated total lifetime exposure to NDMA produced endogenously. Moreover, as discussed above, only a fraction of ingested NDMA molecules are likely to result in mutations, and there is almost certainly a threshold below which NDMA exposure does not result in mutations.

153. When considering maximum theoretical total cumulative exposure to NDMA from ingestion of *any* combination of valsartan product, which was 26.6 mg, if and only if each and every valsartan tablet that they ingested over the entire 1,610-day interval contained the highest measured dose of NDMA in any valsartan product available on the U.S. market on that day. In contrast, estimates of cumulative lifetime endogenous NDMA production based on Hrudey correspond to 26.8 grams of NDMA over a 70-year lifetime. This level of NDMA exposure due to endogenous production is 1,000-times higher than the maximum theoretical total exposure to NDMA due to ingestion of any NDMA-containing valsartan product. Again, this indicates that the maximum theoretical cumulative exposure to NDMA from valsartan products represents – at most – just 0.1% of estimated total lifetime exposure to NDMA produced endogenously.

Theoretical maximum levels of NDMA and/or NDEA exposure from valsartan products are orders of magnitude lower than the lowest levels of NDMA or NDEA observed to cause cancer in experimental animals

154. The maximum level of NDMA measured in any Teva valsartan product was 16.55 ug of NDMA in a 320 mg valsartan tablet, which corresponds to a daily NDMA exposure of 0.000236 mg/kg/d for a 70 kg person. In Peto 1991, the lowest dose of NDMA demonstrated to detectably increase the incidence of cancer in rats was 0.034 mg/kg/d, for biliary cystadenoma.[96,97] On a daily basis, 0.034 mg/kg/d NDMA would correspond to 2,380 ug/d NDMA for a 70 kg person. This daily amount of NDMA determined by Peto is 144-times higher than the highest level of NDMA contained in any lot of any Teva valsartan product.

155. The maximum level of NDMA measured in any valsartan product was 20.19 ug of NDMA in a 320 mg valsartan tablet, which corresponds to a daily NDMA exposure of 0.000288 mg/kg/d for a 70 kg person. Given the lowest daily dose of NDMA demonstrated to detectably increase the incidence of cancer in rats of 0.034 mg/kg/d in Peto 1991,[96,97] which would correspond to 2,380 ug/d NDMA for a 70 kg person, this daily amount of NDMA determined by Peto 1991 is 118-times higher than the highest level of NDMA measured in any lot of any valsartan product.

156. Similarly, when considering total lifetime exposures and cancer risk, lifetime exposure to 0.034 mg/kg/d NDMA in rats would correspond to an exposure of 60,850,650 ug over a 70-year lifetime for a 70 kg person. By comparison, the maximum theoretical total exposure to NDMA to which a Plaintiff could conceivably have been exposed due to ingestion of Teva valsartan products was 22,955 ug. This amount is 2,650-fold lower than the lowest dose of NDMA shown to cause a detectable increase in cancer in rats. Analogously, the maximum theoretical total exposure to NDMA to which a Plaintiff could conceivably have been exposed due to ingestion of *any* combination of valsartan products was 26,635 ug. This amount is approximately 2,280-fold lower than the lowest dose of NDMA shown to cause a detectable increase in cancer in rats. Thus, the maximum theoretical total exposure to NDMA to which a Plaintiff could conceivably have been exposed due to ingestion of *any* combination of valsartan products was still more than three orders of magnitude *lower* than the lowest dose of NDMA shown to cause a detectable increase in cancer in rats.

157. Beyond these reasons, even if one were to assume for the sake of a logical exercise that there is evidence that ingestion of valsartan products resulted in exposure to levels of NDMA that were substantial enough to cause cancer in human beings (there is not), it would still be impossible to rule out other sources of NDMA exposure as a cause, given the many other exogenous sources of NDMA and other nitrosamine exposures, including food, water, air, beer and tobacco, and especially given endogenous levels of production of NDMA that are orders of magnitude higher than any amount of NDMA in the valsartan products to which Plaintiffs could theoretical have been exposed.

158. As above, the highest level of NDEA measured in any lot of any Teva valsartan product was 0.77 ug per tablet.[115] NDEA lifetime carcinogenicity studies in rats by Peto (1991) revealed a no observed effect level for NDEA evident at 0.264 ppm, corresponding to a daily dose of

0.0108 mg/kg/d NDEA for male rats and 0.019 mg/kg/d for female rats.[96,97] That is, rats treated with doses of NDEA as high as 0.0108 mg/kg/d (0.264 ppm) showed no detectable increase in tumorigenesis. A daily dose of 0.0108 mg/kg/d in rats would correspond to 756 ug/d NDEA for a 70 kg person. Thus, the maximum theoretical daily exposure to NDEA from Teva valsartan products was 982-fold (nearly three orders of magnitude) *lower* than a dose of NDEA that did not cause tumors in rats when administered for their entire lifetime.

159. The highest level of NDEA measured in *any* valsartan product was 1.31 ug/tablet.[115] Thus, compared to the observed no effect level of 0.0108 mg/kg/d in rats determined by Peto,[96,97] which corresponds to 756 ug/d NDEA for a 70 kg person, the maximum theoretical daily exposure to NDEA from the valsartan product containing the highest measured level of NDEA was still 577-fold *lower* than a dose of NDEA that did not cause tumors in rats when administered for their entire lifetime.

160. When considering total cumulative exposures, lifetime exposure to 0.0108 mg/kg/d NDEA in rats (the no observed effect level) would correspond to an exposure of 19,329,030 ug over a 70-year lifetime for a 70 kg person. By comparison, the maximum theoretical total exposure to NDEA to which a Plaintiff could conceivably have been exposed due to ingestion of Teva valsartan products was 1,075 ug. Thus, the maximum theoretical cumulative exposure to NDEA from Teva valsartan products was more than 18,000-fold lower than the lowest dose of NDEA shown to cause tumors in rats, if administered over a lifetime. Analogously, the maximum theoretical total exposure to NDEA to which a Plaintiff could conceivably have been exposed due to ingestion of *any* combination of valsartan products was 2,157 ug. This amount is nearly 9,000-fold lower than the lowest dose of NDEA shown to cause a detectable increase in cancer in rats if administered over a lifetime. Thus, the maximum theoretical total exposure to NDEA to which a Plaintiff could conceivably have been exposed due to ingestion of *any* combination of valsartan products was approximately four orders of magnitude *lower* than the lowest dose of NDEA shown to cause a detectable increase in cancer in rats.

Limitations of linear low-dose threshold extrapolation

161. As above, estimates of the ADI for NDMA and NDEA by the FDA, EMA and other agencies were derived based on linear low-dose extrapolation. In effect, linear low-dose extrapolation determines a linear response for very high exposures in the observable dose-response range, and then extrapolates that to very low doses at which effects cannot actually be observed above background. Specifically, in this approach, high levels of NDMA or NDEA are used to identify a dose at which tumors are induced in 50% of rats. Linear extrapolation is then used to calculate the far lower dose that would be predicted to be associated with an increase of only 1 cancer in 100,000 people (0.001% tumor incidence) exposed to that dose over a 70-year lifetime.

162. Critically, this approach relies on the assumption that the dose-response for NDMA and NDEA-induced carcinogenesis remains linear even at extremely low doses. In this regard, it is essential to note that these extremely low doses are many orders of magnitude lower than what is possible to measure, even in experimental animal models. Furthermore, as emphasized above, the maximum theoretical doses of NDMA and/or NDEA to which patients could have

been exposed as a result of ingesting valsartan products are several orders of magnitude lower than the lowest doses of these agents that have been observed to cause cancer. Accordingly, using linear low-dose extrapolation to define an ADI for NDMA (and for NDEA) and estimate cancer risk at these extremely low levels of exposure must, by necessity, encompass the assumptions upon which linear low-dose extrapolation is based. Consequently, an estimate of potential cancer risk attributable to the very low levels of NDMA and NDEA associated with ingestion of valsartan products cannot be based upon direct evidence of cancer risk, even in range of the maximum theoretical exposures to NDMA and NDEA that might have occurred in some patients.

163. There are several important limitations to estimating cancer risk by linear low-dose extrapolation.[79,118,119] First, because no human studies exist that demonstrate a cause and effect relationship between NDMA or NDEA exposure and the development of cancer, this estimation approach is necessarily based on extrapolation from animal studies, rather than human studies. Second, because tumor incidence cannot be measured at such low doses, there is no body of direct evidence to support the linear low-dose-response assumption for NDMA and NDEA at the extremely low doses to which patients could theoretically have been exposed. In fact, as discussed below, there is direct evidence to the contrary, which suggests that the linear low-dose assumption is unlikely to be true for NDMA and NDEA.

164. Fundamentally, linear low-dose extrapolation in this context is based on the assumption that there is no threshold dose below which exposure to NDMA, or NDEA, does not result in an increased risk of cancer. Put another way, this risk estimation approach assumes that exposure to one molecule of NDMA or NDEA is sufficient to increase cancer risk. Indeed, Dr. Panigrahy clearly espouses this belief, upon which he bases his evaluation of whether or not NDMA and/or NDEA can cause cancer in human beings:

> *"Because a genotoxic chemical can permanently induce DNA damage and mutations, there is viewed to be no safe exposure threshold or dose with genotoxic carcinogens[30,31]. This is based on the assumption that even one molecule of genotoxic chemicals may induce a mutation that may cause cancer[31,237]."*[120]

165. The belief that there is no threshold for the carcinogenic effect of genotoxic agents and, therefore, "no safe level" is a fallacy that – as discussed throughout this report – is contradicted by basic tenets of biology, as well as abundant scientific evidence demonstrating thresholds for the carcinogenic and mutagenic effects of agents like NDMA and NDEA that result from the existence of error-free DNA repair systems.[71,80-85] Beyond these scientific reasons, however, even straightforward risk calculations related to the probability of developing cancer in response to a carcinogenic exposure clearly demonstrates the same point – namely, that the proposition that even a single molecule of a carcinogen may cause cancer and therefore cannot be considered safe, defies common sense.

166. For example, Dr. Steven Hrudey discusses cancer risk associated with exposure to 2,3,7,8 tetrachlorodibenzo-*p*-dioxin (TCCD),[121] because it is one of the most potent known carcinogens. Dr. Hrudey calculates based on the potency factor for TCCD q1* $(mg/kg/d)^{-1}$ of 1.56×10^5, which is based on linear extrapolation from the TD50 value (and is therefore a

conservative estimate), administering a dose of one molecule per day of TCCD (corresponding to 0.9 x 10^{-20} mg/kg/d for a 60 kg person) for 70 years (which is 25,550-times higher than exposure to a single molecule) would correspond to a lifetime risk of cancer of 1.4 x 10^{-15}. That is, approximately 1 in 1 quadrillion.[121] To put that in perspective, Dr. Hrudey points out that, if this dose of TCCD were given every day to every person in the world for every person's entire lifetime, there would be less than a 1 in 100,000 chance that anyone on the entire planet would ever develop cancer as a result. This illustrates in the starkest of terms that, while different people might have different definitions of "safe", "under any realistic concept of practicality, there is indeed a safe level of exposure to cancer-causing chemicals".[121]

167. Indeed, even this TCCD estimate is an overestimate, because it is based on linear low-dose extrapolation. As alluded to above, there are several important limitations to estimating cancer risk by linear low-dose extrapolation. First, linear low-dose extrapolation ignores the existence of substantial endogenous (*i.e.*, "background") sources of DNA damage, described elsewhere in this report, that occur as a consequence of the normal physiology of cells. That is, exogenous exposures to very low levels of NDMA and NDEA that would be associated with levels of DNA damage far lower than those that occur endogenously due to normal physiological processes would not be anticipated to yield an observable increase in cancer risk. Moreover, even putting aside the numerous endogenous causes of DNA damage, the maximum theoretical exogenous exposures to NDMA at issue here are orders of magnitude lower than endogenous exposures to NDMA.

168. Second, linear low-dose extrapolation ignores the existence of background exposures to many known mutagens in the environment, such as x-rays, asbestos, and the numerous other chemicals and natural products to which we are all exposed each day. For example, asbestos fibers are nearly ubiquitously present in air. Consequently, we are all exposed to asbestos every day. To estimate these lifetime exposures, the average person breathes in approximately 11,000 liters of air per day, which corresponds to 11 m^3. Using estimates for asbestos fiber content of 100 fibers/cubic meter (f/m^3) in urban settings, the average person would inhale approximately 1,100 asbestos fibers per day, which corresponds to approximately 400,000 asbestos fibers per year.[122] This means that over the course of a 70-year lifespan, the average person lacking any occupational exposure to asbestos would inhale somewhere on the order of 28 million asbestos fibers. In the occupational setting, OSHA regulations call for workplace air concentrations of asbestos to be less than 100,000 f/m^3, which for someone working an 8-hour day would correspond to inhalation of 1.8 million fibers per week, more than 90 million fibers per year, and 3.7 billion fibers of asbestos over the course of a 40-year career, solely due to asbestos exposure during working hours. Thus, inhalation of 28 million – 3.7 billion fibers of asbestos over the course of a lifetime is not associated with a detectable increase in the development of asbestos-related cancers in human beings. This underscores the fallacy of a model that postulates that exposure to a single molecule of a mutagen will increase the risk of cancer, as is implicit in Dr. Panigrahy's report.

169. Third, and especially important, linear low-dose extrapolation ignores the existence of endogenous error-free DNA repair systems, as well as other rate-limiting events required for

the effects of NDMA and NDEA, that result in exposure thresholds for carcinogenic effects below which tumor formation will not occur. As a consequence, low levels of NDMA or NDEA-induced DNA damage that can be repaired by these DNA repair systems prior to DNA replication will not result in mutations and therefore cannot result in carcinogenesis. By definition, then, these repair systems will result in the existence of thresholds for mutation and carcinogenicity for agents such as NDMA and NDEA. Indeed, multiple studies support the existence of a threshold for a no observed effect for a number of mutagenic carcinogens, including alkylating agents such as N-nitroso compounds.[71,79-85,90] As such, it is very likely the case that exposure to very low levels of NDMA and/or NDEA does not result in an increase in mutation frequency, or in carcinogenesis, because the low levels of DNA damage that may be associated with these exposures can be adequately repaired by the endogenous DNA repair systems present in all our cells.

170. These and other considerations imply that the assumptions underlying linear low-dose extrapolation result in inappropriately low, overly conservative estimates for cancer risks at extremely levels of exposure at which effects cannot be measured experimentally.

Epidemiology of valsartan products containing NDMA

171. To date, two epidemiological studies have explored the association between valsartan products containing NDMA and the risk of cancer.[123,124] Pottegard et al. reported a nationwide Danish cohort study based on healthcare system registry data reported no statistically significant elevated overall risk of cancer (HR 1.09 [95% confidence interval [0.85; 1.41]), and no increase in the risk of several individual cancers after exposure to NDMA-containing valsartan drug products with a median follow-up of 4.6 years.[124] These included bladder cancer, breast cancer, colorectal cancer, kidney cancer, lung cancer, melanoma, pancreas cancer, prostate cancer, and uterine cancer. No liver cancers occurred in individuals exposed to NDMA-containing valsartan products. The authors concluded that "the results do not imply a markedly increased short-term overall risk of cancer in users of valsartan contaminated with NDMA," although they noted uncertainty about single cancer outcomes and the need for longer follow-up. Limitations of this study included a relatively small size of 5,150 patients, the reliance of exposure ascertainment on assumptions about NDMA content, and relatively short follow-up.

172. Gomm et al. reported results from a cohort study based on longitudinal data from a German health insurance provider, which included 780,871 people who had filled a prescription of valsartan between 2012 and 2017.[123] They found no association between exposure to potentially NDMA-containing valsartan (in comparison with exposure to valsartan not believed to contain NDMA) and the overall risk of cancer (adjusted HR 1.00, 95% confidence interval [0.98; 1.02]). Nor were associations found between exposure to potentially NDMA-containing valsartan and bladder cancer, breast cancer, colorectal cancer, kidney cancer, lung cancer, malignant melanoma, pancreas cancer, prostate cancer, or uterine cancer. The authors did identify a nominally statistically significant association between exposure to valsartan and hepatic cancer (adjusted HR 1.16, 95% confidence interval [1.03; 1.31], although no dose-dependent effect on the risk of liver cancer was found for higher exposure to potentially NDMA-containing valsartan, and results were not corrected for multiple testing, given that

associations for 10 individual cancers were evaluated. Moreover, Pottegard did not observe any cases of liver cancer in their cohort. Limitations of this study included the inability to rule out residual confounding, the lack of information regarding important risk factors for cancer such as smoking, alcohol and nutritional habits, the lack of information on the precise NDMA content of individual valsartan tablets, and the limited follow-up time of just over 3 years. Importantly, the authors stated that "the present study can only state the existence of a statistical association. Causality cannot be inferred."

173. Despite significant limitations, particularly the short length of follow-up given the mutagenic mechanism of action of NDMA, the above studies do suggest that exposure to valsartan containing NDMA is not associated with a substantial increase in cancer risk within 3 years and 4.6 years, respectively. Notably, this time frame is similar to, if not longer than, that claimed by Dr. Panigrahy in this litigation to be sufficient for NDMA-induced cancers in human beings.[120]

Claimed latencies for Plaintiffs' cancers are too short to be plausibly related to NDMA or NDEA exposure due to valsartan products.

174. As discussed in this report, the vast majority of adult solid cancers are generally believed to develop over a period of 30-50 years. Moreover, estimates of the shortest possible period of time for the development of a clinically detectable cancer following exposure to a mutagenic agent – even though that might only occur in a small minority of cases – is on the order of 11 years or more, as in the case of breast cancer following exposure to ionizing radiation.

175. In contrast to these expectations, which are solidly grounded on decades of research regarding the time frame in which human cancers develop, the latencies for the cancers that Plaintiffs allege in this litigation would be far shorter than what fundamental tenets of cancer biology tell us is possible. Specifically, based on Plaintiff's Fact Sheets for those Plaintiffs who provided dates for first use of valsartan and for cancer diagnosis, it is possible to calculate the time elapsed from the date when that Plaintiff began taking valsartan (irrespective of manufacturer), or the date the first valsartan product potentially containing NDMA became available for purchase in the United States – whichever came last – to the date of their cancer diagnosis. For Plaintiffs in this MDL as of July 19, 2021, this information was available for more than 600 Plaintiffs. Among these, the average time from initiation of use of potentially NDMA-containing valsartan to tumor diagnosis was approximately 3 – 4 years. Moreover, for more than a dozen Plaintiffs, valsartan usage began *after* they were diagnosed with cancer.

176. On its face, for the reasons discussed in this report, the time periods between first exposure to potentially NDMA and/or NDEA-containing valsartan products and diagnosis with cancer for cancers that arose in Plaintiffs are far too short to be plausibly related to the use of NDMA and/or NDEA-containing valsartan products. Rather, it is almost certainly the case that these cancers already existed, but had not yet been clinically detected, prior to the first exposure to NDMA and/or NDEA-containing valsartan products. In short, it is not possible for NDMA- and/or NDEA-containing valsartan products to have caused cancers that were already present. Similarly, based on a wealth of information about the behavior of human primary

cancers, there is every expectation that these subclinical cancers would have come to clinical detection irrespective of valsartan use, with no evidence whatsoever to the contrary.

177. It is also notable that, of the 682 cancers types provided by Plaintiffs as of July 19, 2021, only 11% are cancers of the liver, 9% are cancers of the kidney, 3% are cancers of the esophagus, and less than 1% are cancers of the lung. That is, the types of cancer claimed by Plaintiffs to have been caused by ingestion of valsartan containing NDMA and/or NDEA do not show the same pattern that has consistently been reported in animal studies for high-level NDMA and/or NDEA exposures across animal species: namely, a strong preponderance of liver cancer, with some lung and kidney cancers observed for NDMA exposure, and liver and esophageal cancers observed for NDEA exposure[38]. Thus, only 25% of claimed cancers in Plaintiffs to this point in time are types of cancer that are reproducibly caused in animals by NDMA and NDEA, and none of these types of cancer has a demonstrated association with exogenous exposure to these agents in humans.

178. It is also worth noting that there is no "signature" genetic lesion associated with NDMA or NDEA that would enable a cancer caused by NDMA or NDEA to be reliably identified. This is particularly the case since endogenously formed nitrosamines, including NDMA, result in identical DNA adducts to exogenously ingested NDMA, as do a variety of other agents.

179. In summary, for the reasons discussed throughout this report, I conclude that exposure to NDMA and/or NDEA in valsartan, at the doses to which Plaintiffs were potentially exposed, and for the durations to which Plaintiffs were potentially exposed, does not cause cancer in human beings. Additionally, exposure during the time frames to which Plaintiffs were potentially exposed could not have caused any of the cancers claimed in this litigation. These opinions are based on scientifically valid reasoning and methodology, as I would practice in my daily profession, as well as my education, training, knowledge, and experience, and the materials that I have reviewed in this matter, and is stated to a reasonable degree of scientific and medical certainty.

RESPONSES TO PLAINTIFFS' EXPERTS

Response to Report of Dr. Dipak Panigrahy[120]

Overview

180. The central question at this stage of this litigation is whether exposure to NDMA and/or NDEA *at the doses to which Plaintiffs were potentially exposed via ingestion of valsartan, and within the time frame in which they were potentially exposed*, could have caused the types of cancer in human beings that are claimed in this litigation.

181. Dr. Panigrahy fails to address the question of whether exposure to NDMA and/or NDEA causes cancer in human beings *at the doses to which Plaintiffs were potentially exposed*. Rather, the evidence that he presents is focused almost exclusively on exposures to NDMA and NDEA in experimental animals that are orders of magnitude greater than any exposure claimed

in this litigation. Similarly, Dr. Panigrahy provides no consistent body of evidence demonstrating that NDMA and/or NDEA exposures at the doses to which Plaintiffs were potentially exposed causes cancer in human beings.

182. Dr. Panigrahy also fails to reasonably address the question of whether exposure to NDMA and/or NDEA causes cancer *within the time frame in which Plaintiffs were potentially exposed relative to their diagnoses*. Rather, his claims regarding the exceptionally short period of time from exposure to valsartan potentially containing NDMA and/or NDEA to diagnosis of cancer are contradicted by his own report, and by an overwhelming body of scientific and medical evidence and iron-clad consensus of the scientific community.

183. Dr. Panigrahy refers to IARC, EPA and NTP as "authoritative" agencies, but does not accept their conclusions about the potential carcinogenicity of NDMA and NDEA in human beings. Each of these agencies has classified NDMA and NDEA as "possibly carcinogenic" or "reasonably anticipated to be carcinogenic". None of them have classified either of these agents as a known human carcinogen. In contrast, in reviewing much of the same literature, Dr. Panigrahy claims that NDMA and NDEA <u>are</u> carcinogenic in human beings and, in doing so, reaches a conclusion that no scientific body or regulatory agency has reached, including those agencies that Dr. Panigrahy considers to be "authoritative".

184. Dr. Panigrahy claims that NDMA causes liver cancer, bladder cancer, multiple myeloma, non-Hodgkin lymphoma, leukemia, gastric cancer, small intestine cancer, large intestine cancer, colorectal cancer, rectal cancer, pancreas cancer, esophageal cancer prostate cancer, lung cancer and kidney cancer in human beings. I am not aware of any body of medical or scientific evidence demonstrating that NDMA causes any type of cancer in human beings. Nor does Dr. Panigrahy present evidence that NDMA causes cancer in human beings at the doses to which Plaintiffs in the litigation could conceivably have been exposed as a consequence of ingesting valsartan products. Nor has any regulatory agency concluded that NDMA is a known cause of human cancer.

185. Dr. Panigrahy claims that NDEA causes liver cancer, lung cancer, gastric cancer, blood cancers, esophageal cancer and kidney cancer in animals, but he presents no evidence that NDEA causes cancer in human beings, much less at the doses to which Plaintiffs in the litigation could conceivably have been exposed as a consequence of ingesting valsartan products. Nevertheless, he concluded that NDEA causes human cancers of the liver, lung, stomach, esophagus, kidney, blood, pancreas, bladder, colon, rectum and prostate. I am not aware of any body of medical or scientific evidence demonstrating that NDEA causes any type of cancer in human beings. Nor has any regulatory agency concluded that NDEA is a known cause of human cancer.

Levels of Exposure

186. Dr. Panigrahy does not address the question of whether exposure to NDMA and/or NDEA causes cancer *in human beings at the doses to which Plaintiffs were potentially exposed*. Rather, the evidence that he presents is focused almost exclusively on exposures to NDMA and NDEA in experimental animals. Moreover, these exposures in animals are orders of magnitude

greater than those to which Plaintiffs could conceivable have been exposed as a consequence of ingesting NDMA- or NDEA-containing valsartan products. Furthermore, Dr. Panigrahy provides no consistent body of evidence demonstrating that NDMA and/or NDEA exposure at the doses to which Plaintiffs were potentially exposed causes cancer in human beings. Ironically, the concentrations of NDMA in animal studies that Dr. Panigrahy repeatedly refers to as "low" or "very low" are actually extremely high – orders of magnitude higher than those at issue in this litigation.

187. Indeed, many of the biological effects that Dr. Panigrahy claims for NDMA and NDEA, such as inflammation, immunosuppression, are effects that occur at far higher exposures to NDMA and NDEA than Plaintiffs could have been exposed to, and Dr. Panigrahy provides no evidence that these effects occur in animals exposed to the same range of doses alleged to have occurred in Plaintiffs. This is true for virtually all of the effects discussed, including inflammation, immunosuppression, and carcinogenesis itself. Several of the studies reporting these effects, which Dr. Panigrahy relies upon, were conducted at extremely high, toxic doses of NDMA and/or NDEA that are thousands of times higher than the doses at which these agents induce tumors in experimental animals, and millions of times higher than exposures to NDMA or NDEA to which Plaintiffs could conceivably have been exposed (see below). Such studies do not reliably inform a scientific conclusion about the effects of these agents on the processes in question.

188. Inexplicably, Dr. Panigrahy excludes consideration of the only two epidemiological studies of cancer incidence in patients who ingested valsartan products that potentially contained NDMA and NDEA for the relatively short period of time in which valsartan products potentially containing NDMA and/or NDEA were on the market. That is, he excludes from consideration the two studies of participants who essentially match the Plaintiffs in this litigation. Instead, defying logic, as a basis for his opinions on human carcinogenicity Dr. Panigrahy relies heavily and disproportionately on the Hidajat et al. study of occupational exposure in rubber factory workers,[125] who were exposed to far higher levels of NDMA than Plaintiffs in this litigation, whose route of exposure was different than Plaintiffs in this litigation (inhalation rather than ingestion), who were exposed for far longer periods of time than Plaintiffs in this litigation, and who were simultaneously exposed to multiple agents (rubber dust, rubber fumes, other nitrosamines) to which Plaintiffs in this litigation were not exposed, and which this study claims cause essentially the same set of cancers as high level NDMA exposure. Indeed, it is highly unlikely that the effects of exposure to NDMA in these workers could be isolated from those due to exposure to the other agents reported by these authors to cause a similar set of cancers, much less to accurately measure these exposures. In this regard, I agree with Plaintiffs' expert Dr. Madigan that Hidajat et al. "considered each contaminant (rubber dust, rubber fumes, nitrosamine sum score, NDMA, and NMor) separately so the specific cause of the increased cancer mortality cannot be pinpointed."[126] Moreover, basic, essential factors in this study regarding exposures are unknown, as are smoking history or history of other potentially significant confounding risk factors such as alcohol use, as would be required to draw reliable conclusions.

Latency

189. Dr. Panigrahy's claim that NDMA and NDEA can cause cancer in human beings within a few years, or even months, of exposure is directly contradicted by – and fails to consider – an overwhelming and long-standing body of medical and scientific evidence and consensus of the scientific community that human cancers take decades to develop.

190. Plaintiffs in this litigation allege that their cancers were caused by low dose exposure to NDMA and/or NDEA for short periods of time as a consequence of ingesting valsartan products containing these compounds. Remarkably, though Dr. Panigrahy claims that NDMA and NDEA can cause cancer within a few months, he nevertheless discounts and largely excludes consideration of the only two epidemiological studies of cancer incidence in patients who took valsartan potentially containing NDMA and/or NDEA for relatively short periods of time because the period of follow-up (3 years[123] to 4.6 years[124]) was insufficient. Dr. Panigrahy's contention is internally inconsistent – if NDMA and NDEA can cause cancer in extremely short periods of time (*i.e.*, months to a few years) as Dr. Panigrahy claims, then these two studies do in fact address the central question in this litigation in the very population of patients at issue. If, on the other hand, Dr. Panigrahy claims that 3 – 4.6 years of follow-up, as was reported in these two studies, is too short relative to the natural history of human cancer to be able to identify a significant increase in cancer incidence in patients taking valsartan potentially containing NDMA/NDEA, then this opinion contradicts his own claim – and a central claim of this litigation – that short term exposure to low levels of NDMA and/or NDEA in valsartan products can cause cancer within months or years.

191. Conversely, in order to support his claim that short term exposure of Plaintiffs to extremely low doses of NDMA and/or NDEA by an oral route of administration caused cancers to develop within months to a few years of exposure, Dr. Panigrahy relies almost exclusively on a single occupational study of rubber factory workers who were exposed to extremely high doses of NDMA for many years by a respiratory route.[125] Dr. Panigrahy supports this choice as being driven by the fact that follow-up in this study was 49 years, such that the cancers that occurred in workers could be accurately assessed. In contrast to Dr. Panigrahy's claim in this litigation that NDMA and/or NDEA exposures due to ingestion of valsartan products can cause cancer within months to a few years (time spans that were encompassed by the two valsartan epidemiological studies that Dr. Panigrahy rejected as uninformative due to their "short" follow-up), his choice to rely upon Hidajat et al. suggests the reality of his view – namely his tacit agreement with the overwhelming medical and scientific consensus that human cancers take decades to develop after exposure to a 'cause'. For these reasons, and others, Dr. Panigrahy's claims expressed in his report are internally contradictory, lack logic, and undercut – if not invalidate – his stated opinions in this litigation.

192. Dr. Panigrahy states that "Recent exposure to potent carcinogens…is more likely to be a significant factor in causation that historical exposures". In fact, the opposite would be expected to be true based on our understanding of the mechanisms of action of mutagens and the long latencies for human cancer. For example, for a hypothetical woman exposed to high doses of medical x-rays as an adolescent, and then again as a 50-year old, who is then

diagnosed with breast cancer at age 52, it is undeniably the case that the x-ray exposure that occurred during adolescence would be considered a more "significant" causal factor than the exposure that occurred at age 50, two years prior to diagnosis, in part because this latency is far too short to be plausibly related. I am therefore at a loss to understand the basis for Dr. Panigrahy's counter-intuitive statement, and I find no evidence provided in his report to support this claim, which is contradicted by fundamental tenets of cancer biology.

Tumor Dormancy

193. Dr. Panigrahy's claim that dormant occult tumors are likely to be common and that NDMA activates dormant tumor cells is a postulated mechanism employed to circumvent what is firmly established regarding the long latencies for human cancers, so as to conclude instead that exposure to NDMA can result in the development of human cancers with much shorter latencies (*i.e.*, well under 10 years) that are biologically implausible. In fact, the cancers claimed by Plaintiffs to have been caused by valsartan products containing NDMA and/or NDEA are known to have typically long latencies of several decades or more.

194. The term "dormancy" typically refers to the latency with which tumors recur, not the latency for primary tumor formation. That is, dormancy is thought to occur in residual tumor cells that escape the primary tumor prior to its detection, survive therapy for the primary tumor, and persist in their host for long periods of time prior to emerging as clinically detectable recurrent tumors. Consequently, it is surprising that, throughout his report, Dr. Panigrahy refers to "tumor dormancy escape" as being somehow similar, analogous, or relevant to "cancer induction" by a genotoxic carcinogen. This contention is misleading and incorrect. The concept of tumor dormancy typically refers to microscopic cancer cells that disseminated from a primary cancer to distant sites prior to diagnosis, survived therapy and then exist in a dormant or latent state, but retain the potential to resume growth and give rise to recurrent metastatic cancers, sometimes after many years. Thus, the concept of tumor dormancy refers to properties of disseminated (*i.e.*, metastatic) cancer cells and the kinetics with which they give rise to recurrent metastatic cancers. Accordingly, the existence of dormant disseminated cancer cells and their propensity to give rise to metastatic recurrent cancers does not speak to how long it takes for primary cancers to develop following exposure to a carcinogenic agent.

195. There is no body of evidence that I am aware of that dormancy occurs in primary cancers. Rather, "dormancy" almost invariably refers to "dormancy" in metastatic disseminated tumor cells following the removal and treatment of the primary tumor from which they disseminated.

196. Dr. Panigrahy's speculation about whether exposure to NDMA could cause "dormant" cancers to resume growth would only be relevant in the case of a previously treated cancer patient who subsequently ingested NDMA and then experienced tumor recurrence – which would typically occur at a metastatic site. I am not aware of any Plaintiff in this litigation whose claim is that ingestion of NDMA and/or NDEA-containing valsartan products caused a metastatic recurrence of a previously diagnosed and definitively treated cancer. Moreover, I am not aware of any body of clinical or experimental evidence demonstrating that ingestion of

low doses of NDMA or NDEA cause the reactivation of dormant tumor cells and/or acceleration of tumor recurrence at metastatic sites.

197. Dr. Panigrahy's claim that the identification of "pre-cancerous" lesions or subclinical cancers in tissues from autopsy patients who died of non-cancer related causes provides evidence that these lesions were dormant is surprisingly simplistic and quite clearly incorrect. The existence of "pre-cancerous" lesions or subclinical cancers in tissues from autopsy patients does not imply, or even provide evidence, that these lesions were "dormant". Rather, the identification of pre-cancerous of subclinical cancers in autopsy patients is the simple and inevitable consequence of the decades-long natural history of cancer development in human beings, whereby identifying such lesions in people who die from unrelated causes would be entirely expected. In fact, since dormancy refers to a state of reversible quiescence in disseminated (*i.e.*, metastatic) tumor cells following treatment of a primary tumor, establishing its existence requires demonstration that cells are actually capable of reactivating growth – conditions that cannot be met in autopsy specimens. Rather, Dr. Panigrahy has conflated the actual fact of tumor latency (*i.e.,* tumors take decades to develop in human beings) with his imagined form of primary tumor dormancy in which a subclinical primary tumor exists in a zero net-growth phase that would never have come to clinical detection unless 'reawakened'. There is no body of medical or scientific evidence that I am aware of that such dormant primary cancers exist.

Risk calculations

198. Regulatory limits for acceptable daily intake (ADI) are intended to be extremely conservative. For example, the ADI for NDMA of 96 ng/d was estimated by the FDA to correspond to an incremental risk no higher than 1 additional case of cancer in 100,000 people exposed for 70 years. However, this does not imply that an exposure higher than the ADI will cause harm. Indeed, the FDA has noted that "consuming up to 0.096 micrograms of NDMA of 0.0265 micrograms of NDEA per day is considered reasonably safe for human ingestion based on lifetime exposure."[115] Thus, Dr. Panigrahy's claim that "human cumulative exposure to greater than 96 nanograms per day of NDMA or greater than 26.5 nanograms per day of NDEA increases one's risk of developing cancer" is unsupported by any direct evidence. Indeed, average daily dietary exposures to preformed NDMA are multiples of the FDA ADI, endogenous NDMA production is estimated to be 3 to 4 orders of magnitude higher than the FDA ADI, and the FDA ADI is approximately 25,000-times lower than the lowest dose of NDMA shown to cause cancer in rats.

199. Contrary to Dr. Panigrahy's interpretation, Peto 1991 did not demonstrate that the dose-response to NDMA remains linear at doses substantially below 1 ppm. Indeed, animals dosed with levels of NDMA at 0.033, 0.066, 0.132 and 0.264 ppm did not have an elevated incidence of cancer compared with controls. Rather, Peto assumes that a linear relationship between exposure and cancer incidence observed at high doses is maintained at levels of exposure that are too low to measure any increase at all in cancer incidence relative to background cancer levels in control animals.

200. As articulated elsewhere in this report, linear low-dose extrapolation essentially assumes that one molecule of an agent will cause one mutation. However, if there is DNA repair (which there is), then this assumption is false, such that the rate of mutation will be less than linear at lower doses. Indeed, this is precisely the case for NDMA and NDEA. As discussed in detail above, endogenous enzymes exist that repair the alkylating DNA lesions (*e.g.*, 0^6-methylguanine). Accordingly, at low levels of exposure, DNA adducts may be effectively repaired thereby preventing mutation, and it may not be until the levels of exposure (and, therefore, of adducts) becomes so high as to overwhelm the endogenous system for repairing such lesions, leaving some unrepaired to result in mutation. Even then, such cells may potentially undergo apoptosis. Indeed, the very time courses of DNA adduct levels following exposure discussed by Dr. Panigrahy point to this – after reaching a peak a few hours after exposure, DNA adduct levels subsequently decline, due both to DNA repair and cell death for heavily adduct-affected cells.

"Key" Characteristics of Carcinogens

201. Dr. Panigrahy argues that NDMA and NDEA can be conclusively demonstrated to be human carcinogens based upon how many "key" characteristics these agents share with known carcinogens. This is an oddly indirect argument that circumvents a basic truth. An agent can definitively be considered a human carcinogen if, and only if, it causes cancer in human beings. Similarly, an agent can only be considered an animal carcinogen if, and only if, it can be demonstrated to cause cancers in multiple species of animals. That is the definition of a carcinogen. If an agent cannot be shown to cause cancer, then it cannot be conclusively determined to be a carcinogen. Accordingly, the number of "key characteristics" that NDMA and NDEA may share with known carcinogens cannot provide evidence that NDMA and NDEA are human carcinogens. Moreover, identification of an agent as an animal carcinogen does not mean that it is a meaningful human carcinogen. For example, multiple carcinogens reported to cause tumors in rats and/or mice have not been implicated as likely causes of human cancer[127].

202. The notion advanced by Dr. Panigrahy that the potency of a carcinogen is proportional to the number of "key characteristics" that Dr. Panigrahy estimates that it has (*i.e.*, an agent that possesses 9 key characteristics is a more potent carcinogen than an agent that possesses 4 key characteristics) is without logic or method. The potency of a carcinogen is a quantitative measure determined by how many molecules of that substance are required to cause cancer in a particular experimental system – not by analogy with Dr. Panigrahy's "key characteristics".

203. It is also worth noting that most, if not all, of the "key" characteristics of carcinogens that Dr. Panigrahy cites are characteristics that are also possessed by numerous endogenous molecules. That is, being alive is carcinogenic.

Inflammation

204. Dr. Panigrahy claims that NDMA stimulates chronic inflammation, and that this is a mechanism by which it causes cancer. I am not aware of any body of scientific or medical evidence that NDMA or NDEA causes inflammation at doses comparable to those to which Plaintiffs in this litigation could conceivably have been exposed as a consequence of ingesting

valsartan products. Rather, Dr. Panigrahy relies on studies in experimental animals that used far higher doses of NDMA and/or NDEA than those sufficient to cause tumors in those animals, and far higher still than the amounts of NDMA or NDEA to which Plaintiffs in the litigation could conceivably have been exposed.[128] This fact argues against Dr. Panigrahy's suggestion that the carcinogenic effects of NDMA and/or NDEA in animals are mediated by (hypothesized) effects of these agents on inflammation, since these effects predominantly occur at doses far higher than those causing tumors in animals.

205. Demonstrating that cancers caused by NDMA in experimental animals contain inflammatory cells does not provide evidence that NDMA-induced inflammation causes cancer.

206. Inflammation is a medical term that describes the body's response to injury, and is characterized by an influx of white blood cells from the immune system, changes in the vasculature, redness, heat, pain, swelling and alterations in a variety of cytokines and signaling pathways. Inflammation is ordinarily a protective response that is both beneficial to the organism and essential for life, since it is typically aimed at resolving cellular injury, repairing damaged tissues, and restoring normal tissue function.

207. The immune cells involved in inflammation may include cells of the innate immune system, such as macrophages, neutrophils and eosinophils, as well as cells of the adaptive immune system, such as T and B lymphocytes. As the many cell types and cell-cell interactions involved in the innate and adaptive immune response to inflammation are extraordinarily complex and context-dependent, the term "inflammation" encompasses a broad array of host responses to different types of injuries in different sites in the body that, in turn, may be initiated by a broad array of stimuli. As such, the effects of "inflammation" on any process in question must be studied in the specific context in which it occurs in order to evaluate the various, potentially conflicting effects that it may have.

208. The cells of the immune system constitute an important defense mechanism against the development and growth of human cancers. For example, activation of inflammatory cells by cytokines and cell-cell interactions constitutes an important element of the immune response to abnormal cells and cancer cells, in a process referred to as "immunosurveillance". At the same time, chronic inflammation has been implicated in a number of human cancers. Thus, inflammation is known to have both pro- and anti-tumorigenic effects. Accordingly, the observation that immune cells are present within a tumor does not provide information on the functional consequences of those immune cells on the existing tumor (if any), nor any reliable indication of whether immune cells played any role in the development of that tumor, positive or negative. Indeed, a number of recent studies have revealed that the presence of immune cells within some human cancers is a positive prognostic sign associated with better patient outcome, and their presence has been interpreted as possibly reflecting an immune response against the tumor.

209. For the above reasons, "inflammation" can play both positive and negative roles in human disease. More specifically, the immune system plays both pro-tumorigenic and anti-tumorigenic roles. These interactions are complex and change over time. They are not monolithic.

210. Further highlighting the complex nature of the relationship between inflammation and cancer, chronic systemic inflammatory states are not consistently associated with increased risks of carcinomas. For example, rheumatoid arthritis (RA) is associated with increased systemic levels of pro-inflammatory cytokines such as Tumor Necrosis Factor (TNF), Interleukin 1 (IL-1) and Interleukin 6 (IL-6). Despite this systemic, chronic inflammatory state, RA is associated with a decreased risk of colorectal cancer and breast cancer, and an increased risk of lung cancer. In an analogous manner, Systemic Lupus Erythematosus (SLE) is a chronic inflammatory disease mediated by elevations in pro-inflammatory cytokines, such as TNF, IL-1 and interferons. SLE is associated with a decreased risk of breast, ovarian and endometrial cancer. In contrast, risks of hematologic malignancies, such as leukemias and lymphomas, may be elevated in chronic inflammatory states, such as RA and SLE. As such, the association of chronic inflammation and cancer may be positive, negative, or non-existent and is dependent on cancer type.

211. There is clear evidence that inflammation is caused by cancers. That is, the same mutations within tumor cells that cause cancer also induce changes in the tumor's microenvironment, and these changes may include inflammation.

212. In contrast, while inflammation and the immune system may influence the behavior of human cancers, cancer is fundamentally a genetic disease that is generated and driven by the particular mutations in oncogenes and tumor suppressor genes present within each tumor. I am not aware of any compelling body of scientific evidence that inflammation causes mutations, or is sufficient to cause cancer, in human beings. And even if we were to assume that inflammation did cause cancer, there are many types of inflammation, including obesity, chronic inflammatory conditions, acute inflammatory conditions, responses to physical injury, etc. whose effects could not logically be separated from the inflammation postulated to occur as a consequence of NDMA exposure.

213. Irrespective of generalizations regarding the potential positive or negative effects of inflammation on the development of different types of cancer, it is essential to note that inflammation has not been demonstrated to cause cancer in humans. In this regard, while it is possible that inflammation and the immune system may play positive or negative roles at different stages of tumor development and progression, it is impossible to know what impact these factors may have had, if any, at any specific stage in a particular patient's cancer. Moreover, while inflammation and the immune system may influence the behavior of human cancers, cancer is fundamentally a genetic disease that is generated and driven by the particular mutations in oncogenes and tumor suppressor genes present within each tumor. As such, while it may be difficult, if not impossible, to ascertain what role, if any, inflammation or the immune system may have had on a particular patient's cancer, it clearly is possible to conclude that the mutations present in critical genes within each cell of that cancer are principally responsible for its development and behavior.

214. Nevertheless, to the extent that inflammation may play a role in the development or progression of some human cancers, there are numerous sources of inflammation in humans that impinge on all tissue types at risk for cancer development.

215. As an example of the multiple potential endogenous sources of inflammation in humans, it is now widely appreciated that obesity is associated with a chronic inflammatory state. In this regard, it is also clearly established that obesity is a risk factor for many types of human cancer. The mechanisms underlying the association between obesity and cancer risk have yet to be fully elucidated, but several hypotheses have been proposed. These include hyperinsulinemia and increased bioavailability of insulin-like growth factors, changes in adipokines such as leptin, adiponectin and hepatocyte growth factor (HGF), increased bioavailable estradiol levels, and increased levels of inflammatory cytokines such as IL-6 and TNF-alpha. The levels of several of the above hormones, growth factors and cytokines have been associated with alterations in cancer risk. Further, there are undoubtedly many other biological differences between obese and non-obese individuals that are relevant to cancer etiology and risk that have yet to be elucidated. As such, to the extent that chronic inflammation may play a role in the pathogenesis of human cancers, obesity could not be discounted as a cause of that inflammation.

216. One mechanism by which some Plaintiffs' experts have suggested that inflammation might contribute to carcinogenesis is through reactive oxygen species (ROS) generation by inflammatory cells, which might theoretically contribute to the generation of mutations in non-tumorigenic cells. Importantly, this mechanism is largely, if not entirely, hypothetical as ROS generated by inflammatory cells would have to cross the extracellular space, gain entrance into the cell of origin for cancers, cross the cytoplasm and gain entrance into the nucleus in order to be able to engender DNA damage. Since ROS are generally believed to be very short-lived molecular species, this is highly unlikely to be a substantial source of mutations compared to the abundant ROS that are produced within each cell by mitochondria. As such, to the extent that ROS may contribute to DNA damage and the generation of mutations within human cells, the offending ROS are most likely generated within those cells by mitochondrial processes. Regardless, there is no reliable scientific method by which the relative contributions of ROS produced by mitochondria and ROS produced by inflammatory cells could be ascertained.

Immunosuppression

217. Dr. Panigrahy claims that NDMA causes immunosuppression and that this "key characteristic" contributes to its ability to cause cancer. I am not aware of any body of scientific or medical evidence that NDMA or NDEA causes immunosuppression at doses comparable to those to which Plaintiffs in this litigation could conceivably have been exposed as a consequence of ingesting valsartan practices. Rather, as in the case of his claims regarding inflammation, Dr. Panigrahy relies on studies in experimental animals that used far higher doses of NDMA and/or NDEA than those sufficient to cause tumors in those animals, and far higher still than the amounts of NDMA or NDEA to which Plaintiffs in the litigation could conceivably have been exposed.[129,130] For example, in support of his contention that chronic exposure to NDMA induces "a marked and persistent immunosuppression of cellular and humoral responses in mice", Dr. Panigrahy cites Desjardins et al. (1992).[130] In fact, Desjardins et al. state: "No visible changes in immunological parameters were noted at the 1 ppm NDMA dose."[130], which is a dose that is more than sufficient to induce tumors. Rather, Desjardins et al. only reported immunological suppression in mice at 10-20 ppm NDMA in drinking water,

which the authors note also resulted in the development of ascites, hepatotoxicity, and dose-related mortality as early as 45 days after initiating treatment. These facts, and others, contradict Dr. Panigrahy's suggestion that the carcinogenic effects of NDMA and/or NDEA in animals are mediated by the (hypothesized) ability of these agents to induce immunosuppression, since these effects predominantly occur at toxic doses far higher than those causing tumors in animals.

218. Additional observations corroborate the conclusion that Dr. Panigrahy is, inappropriately, relying upon effects of NDMA and/or NDEA that principally occur at toxic doses of these agents that are far higher than those that cause cancer in animals, and many orders of magnitude higher than levels of NDMA and/or NDEA to which Plaintiffs in this litigation could conceivably have been exposed. For example, from a clinical perspective immunosuppression is typically associated with an increased incidence of cancer only in situations in which immunosuppression is pronounced, if not profound (*e.g.*, pharmacologic immunosuppression post-organ transplantation, advance HIV-AIDS, etc.). Moreover, profound immunosuppression in patients is only associated with certain types of cancers, and these are generally not the common epithelial cancers that Plaintiffs claim were caused by ingestion of NDMA-containing valsartan products. In addition, immunosuppressed patients frequently have clinical symptoms, such as opportunistic infections. I am aware of no body of scientific or medical evidence that patients taking valsartan products containing NDMA or NDEA experienced any biologically meaningful level of immunosuppression.

Oxidative Stress

219. Dr. Panigrahy claims that NDEA induces oxidative stress, and that this "key characteristic" contributes to the ability of NDEA to cause cancer. As with his claims regarding effects of NDMA and/or NDEA on inflammation and immunosuppression, his claims regarding oxidative stress inappropriately rely upon effects of NDMA and/or NDEA that principally occur at toxic doses of these agents that are far higher than those that cause cancer in animals, and many orders of magnitude higher than levels of NDMA and/or NDEA to which Plaintiffs in this litigation could conceivably have been exposed.[131-133] For example, Dr. Panigrahy cites Ajiboye et al.[131] and Bansal et al.[132] as evidence supporting his opinion that NDEA causes oxidative stress. In fact, these studies administered NDEA at doses of either 100 mg/kg or 200 mg/kg to rats. Similarly, Dr. Panigrahy relies upon Bansai et al. to inform his opinion that NDEA creates oxidative stress. This study administered NDEA at a dose of 200 mg/kg to rats. These doses are 10,000 – 20,000-times higher than the lowest NDEA daily dose shown to induce liver tumors in rats, and are 10 – 20 *million* times higher than the highest conceivable dose of NDEA to which Plaintiffs in this litigation could conceivably have been exposed. That Dr. Panigrahy's opinions rely upon studies that use what are quite clearly highly toxic doses of NDEA, millions of times higher than the exposures at issue in this litigation, is scientifically unfounded and inappropriate.

Epigenetics

220. Dr. Panigrahy claims that NDMA induces epigenetic alterations, which he equates (inappropriately) with DNA methylation, and that this "key characteristic" contributes to the

ability of NDMA to cause cancer. The fact that NDMA can methylate DNA bases to generate O^6-methylguanine, N^7-methylguanine, and N^3-methyladenine does not qualify as epigenetic regulation. Rather, epigenetic regulation via DNA methylation typically involves methylation to generate 5-methylcytosine residues, most commonly at CpG dinucleotides. To my knowledge, neither NDMA nor NDEA generate 5-methylcytosine. Thus, these agents do not qualify as epigenetic regulators via an ability to methylate DNA. Furthermore, it bears noting that epigenetic regulation is a normal physiological process. Many epigenetic changes that are believed to play a causal role in cancer are actually mutations in epigenetic regulators. In this way, epigenetic regulators are no different than other oncogenes or tumor suppressor genes in which mutations accumulate in a step-wise manner to result in the development of a cancer cell.

Promotion

221. Dr. Panigrahy claims that exposure to NDMA and/or NDEA at levels present in valsartan products can "critically promote cancer growth". If by "promote cancer growth", Dr. Panigrahy means that NDMA and/or NDEA can cause existing cancers to grow/proliferate more rapidly, I am not aware of any body of medical or scientific evidence that exposure to NDMA or NDEA at levels to which Plaintiffs in this litigation could conceivably have been exposed as a consequence of ingesting valsartan products accelerates the growth of existing cancers. Nor do I find evidence to support this claim provided in Dr. Panigrahy's report.

222. Contrary to Dr. Panigrahy's claim that "continued exposure to NDMA and/or NDEA can cause an existing cancer to grow, metastasize and otherwise interfere with cancer therapy", I am not aware of any body of medical or scientific evidence that exposure of an existing cancer to NDMA and/or NDEA at levels to which Plaintiffs in this litigation could conceivably have been exposed as a consequence of ingesting valsartan products alters the growth rate, metastatic behavior, or response to therapy of existing cancers. Nor do I find evidence to support this claim provided in Dr. Panigrahy's report.

Microenvironment

223. Dr. Panigrahy claims that NDMA and NDEA stimulate tumor progression by acting on the tumor microenvironment. Developing tumors cause changes in their microenvironment that are driven by the same mutant oncogenes and tumor suppressor genes that drive the formation of the cancer. That is, the developing cancer cells cause changes in their microenvironment that are driven by mutations within cancer cells. While the microenvironment can affect existing cancers, affecting a cancer that already exists is not the same as saying that the microenvironment causes the cancer to form. The presumptive carcinogenic mechanism of action of NDMA and NDEA in animals is genotoxicity-induced mutation. These mutations occur in the cells that go on to become tumor cells – not in the stromal cells that compose the microenvironment.

Bradford Hill Analysis

153. First, it must be noted that the evaluation of Bradford Hill criteria cannot be equated with a causal assessment for cancer. This follows from the fact that Bradford Hill criteria principally rely upon epidemiology. While observational epidemiology studies permit inferences regarding causation, they cannot probe cause-and-effect directly. More importantly, this is not 1965 when Sir Austin Bradford Hill outlined his criteria for the inference of causation from epidemiological studies.[134] Our molecular understanding of what causes cancer has dramatically advanced over the past 55 years.

224. These points notwithstanding, Dr. Panigrahy's evaluation of Bradford Hill criteria is fundamentally flawed.

225. Strength: Dr. Hill's criterion of strength of association refers to the strength of association observed in epidemiological studies. Remarkably, Dr. Panigrahy chooses to ignore the only two epidemiological studies[123,124] that precisely correspond to the question at hand – namely, the risk of cancer in patients who took NDMA and/or NDEA-containing valsartan products. If Dr. Panigrahy had included these studies in his evaluation, he would have been forced to conclude that the criterion of "strength" is not met, since neither of these studies identified any significant overall association with cancer. Moreover, the sole finding of a slight increase in liver cancer incidence in one of the studies[123] had an adjusted hazard ratio of only 1.16, which is undeniably weak by any reasonable epidemiological standard. Moreover, no cases of liver cancer in exposed individuals were identified in the second study.[124] Instead of evaluating these studies, Dr. Panigrahy instead chooses to focus on a cohort study of rubber industry workers[125] with occupational levels of exposure to a mixture of agents via inhalation, which would appear to be only tangentially related to question at hand. However, even the subdistribution hazard ratios for this occupationally exposed group of workers were only on the order of 2.0, and many of these were not replicated in other cohort studies of rubber industry workers. In contrast, the examples of risk factors that Dr. Hill provided to illustrate 'strength' were on the order of 200-times (mortality from scrotal cancer in chimney sweeps), 20-30-times (mortality from lung cancer in heavy cigarette smokers), and 14-times (cholera in those drinking polluted water). Moreover, Dr. Hill contrasted these "strong" epidemiological effects with the much weaker death rate from coronary thrombosis in smokers ("no more than twice, possibly less, the death rate in non-smokers"). In discussing coronary thrombosis in smokers, he stated: "Though there is good evidence to support causation, it is surely much easier in this case to think of some features of life that may go hand-in-hand with smoking – features that might conceivably be the real underlying cause or, at the least, an important contributor." Thus, I conclude, based on Dr. Hill's own characterization of strength of association, that NDMA and NDEA fail to meet this criterion.

226. Consistency: Dr. Hill's criterion of consistency refers to the consistency of association observed across epidemiological studies. Dr. Panigrahy first correctly notes that there is a "lack of RCTs and incidental human exposure studies that quantify the exposure to NDMA". However, rather than conclude (as would have been appropriate) that the criterion of consistency is not met, Dr. Panigrahy chooses to evaluate the consistency of the association

between NDMA exposure and cancer in experimental *animal* studies. This criterion refers to epidemiological studies, which Dr. Panigrahy admits are lacking, not animal studies. Thus, I conclude that NDMA and NDEA fail to meet this criterion.

227. Specificity: This criterion refers to whether the association of an agent with cancer is limited to specific workers and/or to particular sites and type of disease. This clearly is not the case for NDMA or NDEA, neither of which has been convincingly demonstrated to be associated with any type of cancer in humans. Moreover, even Dr. Panigrahy admits that he "gave this factor little weight in my causal analysis". Thus, I conclude the NDMA and NDEA fail to meet this criterion.

228. Temporality: Dr. Panigrahy concludes that, since the exposure of patients to NDMA and/or NDEA-containing valsartan occurred prior to cancer development, then this criterion is met. In contrast to his evaluation, since no human cancer has been reliably demonstrated to be associated with NDMA and/or NDEA exposure, temporality cannot possibly be met. Moreover, even in the case of patients consuming NDMA and/or NDEA-containing valsartan products, the time elapsed from first exposure to cancer diagnosis, as claimed by Plaintiffs, is far too short to have satisfied this criterion.

229. Biological gradient: This criterion refers to the presence of a dose-response in epidemiological studies. Dr. Panigrahy concludes that animal studies, and the Hidajat occupational cohort study of rubber industry workers, show a dose-response. Of course, Dr. Hill's criterion refers to epidemiology studies, not animal studies. Moreover, as above, since no human cancer has been reliably demonstrated to be associated with NDMA and/or NDEA exposure, the dose-response criterion cannot be met. Indeed, even the one isolated, albeit weak, finding of an association between ingestion of valsartan containing NDMA and liver cancer was noted to <u>not</u> have a dose-response.[123] Thus, I conclude that this criterion is not met.

230. Plausibility: As Dr. Hill notes, "what is biologically plausible depends upon the biological knowledge of the day." In this regard, Dr. Panigrahy's theory that short-term exposure to NDMA and/or NDEA containing valsartan products can cause the development of cancers in human beings within a period of months, or a few years, violates basic, well-established, universally accepted facts regarding cancer biology and the natural history of human cancer. It is worth noting that in evaluating biological plausibility, existing scientific and medical knowledge are used to evaluate the likelihood that a new hypothesis is true, particularly as it relates to evaluating whether a cause-and-effect relationship exists between a biological factor of interest and a particular disease. Consequently, for a proposed causal relationship to be biologically plausible, not only must a hypothesized mechanistic link between two factors be deemed to be conceivably true, there must also be coherent evidence that the proposed mechanism is true, as well as an absence of a significant body of evidence suggesting that it is not true. Consequently, although the mechanism of action of NDMA and NDEA as alkylating agents is a plausible mechanism, if exposed at a sufficiently high dose, the notion that NDMA and/or NDEA cause cancer at doses that are orders of magnitude lower than the lowest dose observed to cause cancer in experimental animals is decidedly implausible. Moreover, as

discussed in this report, beyond the lack of evidence that NDMA and/or NDEA are human carcinogens, even more so at the extremely low doses to which Plaintiffs could conceivably have been exposed as a consequence of ingesting valsartan products, the claim that NDMA and/or NDEA cause the development of cancers in human beings within months or a few years is clearly biologically implausible. Thus, based on the weight of evidence, I conclude that this criterion is not met.

231. Coherence: Dr. Hill explains that this criterion is predicated on the axiom that "the cause-and-effect interpretation of our data should not seriously conflict with the generally known facts of the natural history and biology of the disease." The ability of NDMA and NDEA to cause cancer in experimental animals when administered at sufficiently high doses can be taken as some evidence of coherence. However, other evidence cited above, particularly with respect to temporality, dose and biological plausibility, argue against coherence.

232. Experiment: This criterion asks whether a preventive action taken has a protective effect. I agree with Dr. Panigrahy that there is no such evidence that would satisfy this criterion for NDMA or NDEA.

233. Bradford Hill's summary of his criteria is that "none of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a *sine qua non*. What they can do, with greater or less strength, is to help us to make up our minds on the fundamental question – is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?" In fact, in my opinion, the answer to this summary question for NDMA and NDEA is 'yes'. Namely, that there are other more straightforward ways of explaining the set of facts. And these are that the cancers in question that were diagnosed in Plaintiffs were already present at the time of exposure to NDMA and/or NDEA-containing valsartan products and that these cancers are simply common human cancers that arise as a consequence of aging and other factors unrelated to exogenous NDMA and/or NDEA exposures. Moreover, the doses and durations of NDMA and/or NDEA to which Plaintiffs could conceivably have been exposed are far too low and for far too short a duration to have plausibly caused cancer. Additionally, the time frame within which these cancers were diagnosed relative to any exposures related to NDMA and/or NDEA-containing valsartan is far too short to be plausibly related to these exposures.

Response to Report of Dr. Stephen Lagana[135]

234. I strongly disagree with Dr. Lagana's claim, unsupported by any citation to evidence, that "it is probable that individuals who are predisposed to cancer for any reason (genetic or environmental) have an even greater likelihood of developing cancer following and in part as a result of ingestion of NDMA or NDEA at the levels established for the contaminated valsartan." I am not aware of any body of evidence whatsoever that would support Dr. Lagana's contention that individuals who are predisposed to cancer for any reason have a greater likelihood of developing cancer as a result of exposure to NDMA or NDEA at the levels to which Plaintiffs in this litigation could conceivably have been exposed.

235. In responding to his specific claim that NDMA and NDEA-induced carcinogenesis in human beings is amplified in individuals who are predisposed to cancer, we must start with the observation that NDMA and NDEA have not been demonstrated to be human carcinogens, nor are they considered so by any regulatory agency that I am aware of, nor has oral exposure to these agents been reproducibly associated with any type of human cancer, much less at the extremely low levels to which Plaintiffs in this litigation could conceivably have been exposed. Consequently, if there is a lack of clear evidence that NDMA and NDEA are human carcinogens, how can there be evidence of a synergistic interaction between their hypothesized carcinogenic effects in humans with genetic susceptibility? Indeed, there is not. In fact, there is evidence to the contrary to Dr. Lagana's unsupported, proposition that inherited susceptibility to cancer amplifies the effects of hypothesized carcinogenic agents. As a general matter, inherited mutations in tumor suppressor genes that are associated with a major increase in risk of a particular type of cancer do not necessarily modify the effect (termed an "interaction") of environmental or behavioral risk factors that are observed in the general population for that same type of cancer. For example, although inherited mutations in *BRCA1* are associated with a major increase in the risk of developing breast cancer, and although long-term use of hormone replacement therapy has been reported by some to be associated with an increase in the risk of being diagnosed with breast cancer, available evidence suggests that women with inherited mutations in *BRCA1* who are treated with hormone replacement therapy are not at an increased risk of developing breast cancer compared to *BRCA1* mutation carriers who are not treated with hormone replacement therapy.[136] Further, Dr. Lagana's claim that this imagined amplifying effect of NDMA and NDEA exposure extends to people who have increased susceptibility to cancer "for any reason" is particularly surprising and so broad as to border on the bizarre. There are numerous inherited cancer susceptibility syndromes. To my knowledge, there is not a single one of these for which any body of evidence exists demonstrating that people with that inherited susceptibility have an increased risk of developing cancer in response to NDMA and/or NDEA exposure. Nor does Dr. Lagana provide any such evidence. For these reasons, Dr. Lagana's claim that people with any inherited susceptibility to cancer are more susceptible to carcinogenic effects of NDMA and/or NDEA is scientifically unfounded.

236. I disagree with Dr. Lagana's contention that cancer risk in human beings associated with mutagenic effects of NDMA and NDEA "is likely greater in organs in which the cells replicate frequently (e.g. gastrointestinal tract)." Indeed, there is substantial evidence to the contrary. As discussed in this report, current scientific thinking does not support the notion that the more rapid the rate of proliferation in a tissue, the greater the likelihood of that tissue developing cancer. For example, cell proliferation rates in bone marrow are amongst the highest in the human body, but cancers of bone marrow cells are quite rare compared to cancers of tissues with far lower proliferation rates, such as the lung and breast. While it is true that DNA damage cannot be 'fixed' (*i.e.*, become permanent) as a mutation until DNA replication has occurred, this in no way implies that the faster the rate of proliferation in a tissue, the more susceptible it is to mutagens. Indeed, as noted elsewhere in this report, the same factors that stimulate cells to proliferate also turn on the expression of DNA damage sensing and repair proteins, as well as a host of other proteins that regulate cell cycle progression in the context of DNA damage (thereby giving cells with DNA damage more time to repair it). Thus, there is no compelling

body of evidence to support Dr. Lagana's hypothesis that increased rates of proliferation necessarily decreases the overall efficiency of DNA repair. Similarly, Dr. Lagana's claim that the effects of mutagens are greatest in rapidly proliferating tissues is also scientifically unfounded. Indeed, one need only look as far as the present case. If Dr. Lagana's hypothesis was true, we would expect the effects of NDMA and NDEA in experimental animals to be greatest in those tissues with the highest rates of proliferation. This is obviously not the case. The liver is clearly the most sensitive site for tumorigenesis in experimental animal models treated with NDMA or NDEA. Yet the liver is most certainly not a tissue with a high proliferation rate and has far lower proliferation rates than other tissues that do not reproducibly give rise to cancers in NDMA- or NDEA-treated experimental animals. Given the fact that liver cells are considered to be long-lived, quiescent cells with extremely low rates of proliferation,[137] Dr. Lagana's proposition is, on its face, untenable. Moreover, a variety of other evidence exists indicating that proliferation is not intrinsically linked to cancer risk, even in the presence of mutations. One example of this is the observation that pregnancy – which is associated with an enormous increase in cellular proliferation in the breast – nevertheless protects against breast cancer even in women who have been exposed to a mutagenic agent, such as was the case with women exposed to ionizing radiation during the atomic bomb blasts at Hiroshima and Nagasaki. For these and other reasons, Dr. Lagana's claim is contradicted by a wealth of scientific and medical literature.

237. I disagree with, and am puzzled by, Dr. Lagana's statement that: "the crucial point is that we start from the assumption that exposure to a human carcinogen contributed to carcinogenesis in a patient with a cancer unless there is convincing evidence to the contrary." Proving that NDMA and/or NDEA exposure associated with ingestion of valsartan products contributed to carcinogenesis in a human being, cannot logically begin with an assumption that it did. That is, in my opinion, as circular as an argument can be. Moreover, Dr. Lagana's added caveat (*i.e.,* "unless convincing evidence to the contrary is available") quite literally indicates his opinion that his assumption is true unless definitively proven otherwise. This approach flies in the face of the scientific method. It simply does not comport with the scientific method to assume that an exposure caused cancer in a patient, unless proven otherwise. Rather, the scientific method dictates that the focus of inquiry must be on whether there is, or is not, proof that the agent is carcinogenic in human beings. Irrespective of this basic tenet, Dr. Lagana's reasoning is illogical. As discussed elsewhere in this report, we are all exposed to many known human carcinogens every day, including ionizing radiation, asbestos and a variety of chemicals present at low levels in our water, food, and the air we breathe. By Dr. Lagana's reasoning ("we start from the assumption that exposure to a human carcinogen contributed to carcinogenesis in a patient with a cancer"), we should consider most, if not all, of these carcinogens to have contributed to any individual cancer. Indeed, Dr. Lagana would have us extend this to agents that have not even been demonstrated to be known human carcinogens. In my opinion, this is a logically untenable proposition that is unsupported by any reliable medical or scientific method.

238. I disagree with Dr. Lagana's statement that: "in medicine, a 46% increased risk is a strong association, thus fulfilling the first of Bradford Hill's criteria (strength of association)." 46% (*i.e.*, RR 1.46) is not a "strong" association. As a comparison, tobacco smoking is associated with a 2,000%-10,000% increase in lung cancer risk, as Dr. Lagana himself notes. By

comparison, 46% increase in risk is weak; indeed, a RR of 1.46 would mean that, for any patient diagnosed with a cancer, the odds would be only 1 in 3 that the cancer was related to such a risk factor – even if we were to assume that a risk factor is a cause, which it is not. As discussed elsewhere in this report, the examples of risk factors that Dr. Hill provided to illustrate 'strength' were on the order of 200-times (mortality from scrotal cancer in chimney sweeps), 20-30-times (mortality from lung cancer in heavy cigarette smokers), and 14-times (cholera in those drinking polluted water). Moreover, Dr. Hill contrasted these "strong" epidemiological effects with the much weaker death rate from coronary thrombosis in smokers, which he characterized as "no more than twice". Thus, Dr. Hill himself directly refutes Dr. Lagana's contention that a relative risk of only 1.46 is "strong" and fulfills the Bradford Hill criterion for strength of association.

239. I strongly disagree with Dr. Lagana's statement: "it is worth noting that once a carcinogen has entered the bloodstream, it is likely that it can cause cancers in nearly any organ. It would be difficult for one to scientifically exclude the potential for a bloodborne carcinogen to cause cancer in any organ to a reasonable degree of medical certainty." There is no scientific or medical basis for this statement that I can discern, and it is flatly contradicted by 50 years of observations. The tissue-specificity for effects of carcinogens, and of genetic alterations, is well known, whereby each known chemical carcinogen is preferentially associated with an increase in cancer risk in one or more tissues. As a case in point, the carcinogenic effects of NDMA and NDEA in experimental animal models are largely confined to the liver, with some evidence for increases in cancer in lung, kidney and esophagus. These agents clearly enter the bloodstream, and therefore contradict Dr. Lagana's claim that these agents somehow cause cancer in all tissues. Indeed, the tissue-specificity of carcinogenic effects of NDMA in experimental animals has been recognized for decades. But one example of this can be found in the 1989 ATSDR review of NDMA:

> *"The carcinogenic properties of NDMA, and nitrosamines in general, have been extensively studied. It is of considerable interest that, despite its ubiquitous distribution, NDMA induces tumors in a limited number of organs and tissues…."*[16]

240. There are numerous other examples – beyond NDMA and NDEA – of the fallacy of Dr. Lagana's simplistic claim that access to an organ or tissue by a carcinogen (*i.e.*, by entering the bloodstream) is tantamount to the ability of that carcinogen to cause cancer in that tissue. Cigarette smoking is associated with entry into the bloodstream of multiple carcinogens. Yet even cigarette smoking is accepted as a cause of only a relatively small set of cancer types. As another example, a variety of chemotherapeutic agents are mutagenic and are given intravenously to cancer patients. In some cases, these agents are associated with an increase in the subsequent risk of a "secondary" cancer in one or a few tissues, but I am not aware of any chemotherapeutic agent that is believed to cause cancers in every tissue in human beings when administered intravenously. Indeed, I do not know of any carcinogen that could reasonably be considered to be "universal" (*i.e.*, causes cancer in all tissues). The tissue specificity of carcinogens is mirrored by the tissue specific effects of genetic mutations. For example, inherited mutations in critical tumor suppressor genes, like *TP53*, *RB*, *BRCA1* and *BRCA2*, give rise to increased risks of cancer that are restricted to only a few specific tissues. For example,

people who inherit mutations in the RB tumor suppressor are at a markedly increased risk of developing retinoblastoma, pinealoma, osteosarcoma and melanoma, but not other cancer types. That is, despite the fact that these tumor suppressors are expressed in, and play a critical regulatory role in, virtually every cell type in the body, their mutation in every cell in the body results in very limited sets of cancers that are restricted to certain tissues. While the molecular basis for this tissue specificity is often not known, what is clear is that there is no such thing as a chemical agent, or even a gene mutation, that causes cancer in all tissues, as Dr. Lagana contends.

Summary of Conclusions

- Human cancers are a heterogeneous collection of distinct, multifactorial diseases with many etiologies and numerous associated risk factors.

- Cancers arise from an accumulation of mutations in the DNA sequence of multiple critical regulatory genes within the same cell. It is typically not possible to determine the cause of a person's cancer, beyond the mutations contained within it, and it is impossible to rule out endogenous processes as the cause of those mutations.

- Before a normal cell can become "cancerous", it must accumulate a set of mutations in critical regulatory genes that is sufficient to overcome its normal physiological regulation and drive uncontrolled cell proliferation and cell survival, induce the formation of new blood vessels, and confer the abilities to proliferate indefinitely and to invade tissue and metastasize to distant sites in the body. This is generally understood to require mutations in at least six different critical genes.

- Mutations most commonly occur in the absence of any environmental exposure to a carcinogen, because our DNA is constantly being damaged as a consequence of the normal functioning of our cells. Critically, however, DNA damage does not necessarily result in mutations, because mutations do not occur until a cell replicates its damaged DNA. Fortunately, our cells have DNA repair mechanisms that can remove DNA damage and restore its DNA sequence to an error-free state before the cell replicates its DNA. In particular, DNA repair enzymes exist in our cells that are able repair the precise type of DNA damage caused by NDMA and NDEA. In addition, our cells have still other safeguard mechanisms that can delay or halt a damaged cell's progression through the cell cycle to allow time for DNA repair to occur prior to DNA replication, or that can initiate a self-destruct mechanism to eliminate an irretrievably DNA-damaged cell from the body. Together, these physiological mechanisms prevent mutations from occurring following DNA damage.

- Because of the DNA repair and cell safeguard mechanisms discussed herein, there is often a threshold of low-level DNA damage below which mutations do not occur, because that level

of DNA damage can be repaired. In particular, it is almost certainly the case that a threshold exists below which NDMA and/or NDEA exposure do not result in mutations.

- The process of acquiring sufficient mutations for a normal cell to transform into a cancerous cell is generally understood to take decades, which is why cancer is overwhelmingly a disease of older persons. Further, there is no reliable scientific method for determining precisely when a first cancer cell arose in an individual patient.

- NDMA and NDEA are N-nitroso (nitrosamine) compounds, which are found in food, tobacco, air, drinking water, soil, and as a byproduct of industrial process. Accordingly, they are ubiquitous in our environment. Even more importantly, our bodies produce large quantities of nitrosamines every day, including NDMA. Endogenously formed nitrosamines are increasingly understood to be a major — if not the major — source of human nitrosamine exposure. Endogenous daily NDMA exposure is estimated to be approximately 1,875-times higher than the highest estimate of exogenous daily exposure to NDMA in food, water and air, and nearly 11,000-times higher than the FDA ADI of 0.096 ug/d.

- Although NDMA and NDEA are known carcinogens in laboratory animals, they are not known carcinogens in humans. No cancers in humans have been conclusively demonstrated to result from exposure to NDMA or NDEA and there is no reliable scientific basis to conclude that either NDMA or NDEA is a human carcinogen.

- Linear low-dose extrapolation models from animal studies, such as those employed by FDA in setting its ADI levels for NDMA/NDEA, are not supported by direct evidence for human carcinogenicity, and ignore background exposures, endogenous exposures, error-free DNA repair mechanisms, and other rate-limiting events.

- The maximum theoretical total amount of NDMA to which any Plaintiff might conceivably have been exposed through valsartan is approximately 1,000-times lower than the amounts of NDMA produced endogenously. Moreover, the maximum theoretical total amounts of NDMA and NDEA to which any Plaintiff might conceivably have been exposed through valsartan are approximately 2,000- and 9,000-times lower, respectively, than the lowest doses shown to cause cancer in animal studies.

- As such, it is my conclusion, to a reasonable degree of medical and scientific certainty, that exposure to NDMA and/or NDEA in valsartan, at the doses to which Plaintiffs were potentially exposed, and for the durations to which Plaintiffs were potentially exposed, would not cause cancer in human beings.

- The only existing epidemiological data to examine human exposure to valsartan containing the NDMA/NDEA impurity support this conclusion. Gomm et al. and Pottegard et al. showed no increase in the risk of bladder cancer, breast cancer, colorectal cancer, kidney cancer, lung cancer, melanoma, prostate cancer, or uterine cancer. Gomm found a statistically significant association between exposure to valsartan containing the impurity and liver cancer, but no dose-dependent effect was observed, the study did not control for

other risk factors for liver cancer, and it did not correct for multiple testing (*i.e.*, testing for an association for multiple types of cancer, one type at a time), which most likely would have rendered the result statistically insignificant. Most importantly, the authors themselves concluded from their study that: "Causality cannot be inferred."

- The known latency periods associated with the cancers claimed by Plaintiffs in this litigation are also too long for Plaintiffs to have developed the claimed cancers within 3-4 years of exposure to NDMA or NDEA, as they necessarily claim.

- The expert reports offered by Drs. Panigrahy and Lagana put forth numerous claims that are unsupported by citation to reliable evidence, are flatly contradicted by available scientific and medical evidence and by our current understanding of the biology of cancer development, and are logically and scientifically flawed.

These are my opinions concerning this matter, and I have a sufficient factual basis and good grounds for my conclusions. They are given to a reasonable degree of scientific and medical certainty, and are based on my training and experience and review of the materials included on Exhibit B. I reserve the right to modify this report as additional information is provided to me, including but not limited to additional medical records and the depositions of Plaintiff's experts which are ongoing.

I may use at trial any exhibits as a summary or in support of all of my opinions including: (1) any of the materials, or excerpts identified in this report and attachments, including the materials considered list; (2) excerpts from scientific articles or learned treatises; (3) demonstrative models; (4) exhibits used by Plaintiffs' experts, or other witnesses; (5) any exhibit used in or identified at any deposition taken in this litigation. If further data becomes available, I will review it and consider whether to modify any portion of these opinions.

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Date: September 24, 2021

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CHODOSH

EXHIBIT A

UNIVERSITY OF PENNSYLVANIA – SCHOOL OF MEDICINE
Curriculum Vitae

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If you are not a U.S. citizen or holder of a permanent visa, please indicate the type of visa you have:
None (U.S. citizen)

Education:

1977-81	B.S.	Yale University (Molecular Biophysics and Biochemistry)
1981-89	M.D.	Harvard Medical School
1983-88	Ph.D.	Massachusetts Institute of Technology (Biochemistry) Laboratory of Dr. Phillip Sharp

Postgraduate Training and Fellowship Appointments:

1989-90	Intern in Medicine, Massachusetts General Hospital, Boston, MA
1990-91	Resident in Medicine, Massachusetts General Hospital, Boston, MA
1991-94	Clinical Fellow in Endocrinology, Endocrine Division, Massachusetts General Hospital, Boston, MA
1991-94	Clinical Fellow in Medicine, Harvard Medical School, Boston, MA
1992-94	Research Fellow in Endocrinology, Endocrine Division, Massachusetts General Hospital, Boston, MA
1992-94	Research Fellow in Medicine, Harvard Medical School, Boston, MA
1992-94	Postdoctoral Research Fellowship, Department of Genetics, Harvard Medical School, Boston, MA Laboratory of Dr. Philip Leder

Military Service

[none]

Faculty Appointments:

1994-2000	Assistant Professor of Molecular and Cellular Engineering University of Pennsylvania School of Medicine
1994-2000	Assistant Professor of Medicine (secondary) Division of Endocrinology, Diabetes and Metabolism University of Pennsylvania School of Medicine
2000-02	Associate Professor with Tenure Department of Molecular and Cellular Engineering

	University of Pennsylvania School of Medicine
2000-06	Associate Professor with Tenure, Department of Medicine Division of Endocrinology, Diabetes and Metabolism (secondary) University of Pennsylvania School of Medicine
2002-06	Associate Professor with Tenure, Department of Cancer Biology University of Pennsylvania School of Medicine
2002-06	Associate Professor with Tenure Department of Cell & Developmental Biology (secondary) University of Pennsylvania School of Medicine
2006-	Professor, Department of Cancer Biology University of Pennsylvania School of Medicine
2006-	Professor, Department of Medicine (secondary) Division of Endocrinology, Diabetes and Metabolism University of Pennsylvania School of Medicine
2006-	Professor, Department of Cell & Developmental Biology (secondary) University of Pennsylvania School of Medicine
2007-08	Interim Chairman, Department of Cancer Biology University of Pennsylvania School of Medicine
2008-12	J. Samuel Staub, M.D. Endowed Professor University of Pennsylvania School of Medicine
2008-	Chairman, Department of Cancer Biology University of Pennsylvania School of Medicine
2018-	Perelman Professor in Cancer Biology (Endowed Chair) University of Pennsylvania

Hospital and Administrative Appointments:

1994-	Member, Abramson Cancer Center, University of Pennsylvania School of Medicine
1995-	Attending Staff Physician, Hospital of the University of Pennsylvania
2000-	Member, Center for Developmental Biology, University of Pennsylvania School of Medicine
2002-	Associate Investigator and Investigator, The Leonard and Madlyn Abramson Family Cancer Research Institute at the University of Pennsylvania Cancer Center
2002-07	Vice Chair, Department of Cancer Biology University of Pennsylvania School of Medicine
2004-08	Founding Co-Director, University of Pennsylvania Small Animal Imaging Facility
2004-	Director, NCI-UPENN Mouse Models for Human Cancers Consortium
2005-13	Program co-Leader, Breast Cancer Program Abramson Cancer Center
2005-16	Director, Cancer Genetics Abramson Family Cancer Research Institute
2016-	Director, Tumor Biology Abramson Family Cancer Research Institute
2005-10	Director, UPENN DOD Breast Cancer Center of Excellence
2005-	Executive Committee

	Abramson Family Cancer Research Institute
2005-	Executive Committee, Abramson Cancer Center
2006-	Associate Director for Basic Science, Abramson Cancer Center
2007-08	Interim Chairman, Department of Cancer Biology
2008-	Chairman, Department of Cancer Biology
2012-	Co-Director, 2-PREVENT Translational Center of Excellence

Medical Licensure: Massachusetts and Pennsylvania

Specialty Certification:

1992-2002	Diplomate in Internal Medicine, American Board of Internal Medicine
1997-2007	Diplomate in Endocrinology and Metabolism, American Board of Internal Medicine

Awards, Honors and Membership in Honorary Societies:

1977	National Merit Scholar
1977	Cornell Ingenuity in Mathematics and Science Award
1977	Harvard Book Prize
1977	Bausch and Lomb Honorary Science Award
1981	*Summa cum laude*, Yale University
1981	Phi Beta Kappa, Yale University
1981	Distinction in Molecular Biophysics and Biochemistry Yale University
1981	Emerson Tuttle Cup for Distinguished Academic Achievement Yale University
1983-89	Medical Scientist Training Program, Harvard Medical School
1985	Leland Fikes Foundation fellow
1989	Leon Reznick Memorial Prize for Excellence in Research Harvard Medical School
1989	Soma Weiss Research Assembly Award, Harvard Medical School
1989	*Magna cum laude*, Harvard Medical School
1992-94	Merck Research Laboratories MD-PhD Fellowship
1996-99	Charles E. Culpeper Foundation Scholarship in the Medical Sciences
1998-2002	U.S. Army Breast Cancer Research Program Career Development Award
2002	AACR-Sidney Kimmel Symposium for Cancer Research Scholar Award
2002	American Society for Clinical Investigation
2005-10	Director, DOD-UPENN Breast Cancer Center of Excellence
2008	Member, Interurban Clinical Club
2008	Association of American Physicians
2009-12	J. Samuel Staub, M.D. Endowed Professor
2013	Dept of Cancer Biology Award for Excellence in Teaching
2017	National Academy of Medicine

2018 Perelman Professor in Cancer Biology

Memberships in Professional and Scientific Societies:

National Societies:

American Society for Clinical Investigation
Association of American Physicians
National Academy of Medicine
American College of Physicians
American Association for Cancer Research
Endocrine Society
American Association for the Advancement of Science
Society for Developmental Biology
American Society for Microbiology
FASEB

Local Societies:

Massachusetts Medical Society

National Scientific Committees:

Electorate Nominating Committee, American Association for the Advancement of Science (2020 -)

Scientific Committees:

Nurses' Health Study I and II, Harvard Medical School, Boston, MA
External Advisory Committee (1998-2016)
Breast Cancer Program Project Grant, Baylor College of Medicine
External Advisory Committee (2002-2007)
CNGI Center Grant, University of Alabama, Birmingham
External Advisory Committee (2002-2004)
Georgetown Cancer Center, Breast Cancer Program Project Grant
External Advisory Committee (2003-2004)
Fox Chase Cancer Center, Breast Cancer and Environmental Research Center, External Advisory Committee (2003-2007)
Dana Farber/Harvard Cancer Center Scientific Advisory Board (2013-present)

Editorial Positions:

1999-2000	Editorial Board, *Breast Cancer Research*
2001-2012	Editorial Board, *Journal of Mammary Gland Biology and Neoplasia*
2003-2014	Associate Editor, *Cancer Biology & Therapy*
2001-2004	Deputy Editor, *Breast Cancer Research*
2005-2008	Senior Editor, *Breast Cancer Research*
2008-present	Editor-in-Chief, *Breast Cancer Research*
2010-2013	Senior Editor, *Cancer Research*

Ad Hoc Reviewer:
Nature, Cell, Science, New England Journal of Medicine, Nature Genetics, Nature Medicine, Cancer Cell, Science Translational Medicine, Molecular & Cellular Biology, Proceedings of the National Academy of Sciences USA, Lancet,

Cancer Research, Development, Human Molecular Genetics
Developmental Biology, Molecular Endocrinology, Oncogene

Peer Review Panels:

1995, 96, 98	U.S. Army Breast Cancer Research Program -
1997, 98, 2000	Susan G. Komen Breast Cancer Foundation
1998, 99	Concert for the Cure
2000	Massachusetts Dept of Public Health Breast Cancer Research Program
2001, 2004	California Breast Cancer Research Program (Chair, 2004)
2009-2012	Cancer Prevention Research Institute of Texas (CPRIT)
2015-2017	AACR Breast Cancer Research Grants Scientific Review Committee
2018	Stand Up To Cancer Canada Metastatic Breast Cancer Peer Review Committee
2019-2020	AACR Outstanding Investigator Award Selection Committee

Academic Committees at the University of Pennsylvania and Affiliated Hospitals:

1994-1996	Internal Advisory Committee, Institute for Human Gene Therapy
1994-1998	Hematology/Immunology Faculty Search Committee, Institute for Human Gene Therapy
1995-1996	Departmental Review Committee - Department of Pediatrics
1995-	Admissions Committee, Combined Degree Program
1997-1998	Departmental Review Committee, Department of Pathology and Laboratory Medicine
1999-2000	Short Term Experience in Research Advisory Committee
1999	Internal Advisory Committee, Cancer Clinical Epidemiology Training Grant, Clinical Center for Epidemiology and Biostatistics
1999-2000	Review Committee, Graduate Group in Neuroscience
2000	LCME Basic Science Task Force
2000-present	Mentoring Program, Combined Degree Program
2002-03	Chair, Cancer Center Working Group on Animal Imaging
2003-2005	Committee on Academic Freedom and Responsibility
2004-2005	Faculty Search Committee for Chair Department of Radiation Oncology
2004-2006	Faculty Search Committee for Chief, Division of Nuclear Medicine
2007	Faculty Search Committee for Chair, Department of Medicine
2008	Faculty Search Committee for Chief, Division of Hematology/Oncology
2010	Faculty Search Committee for Director, Abramson Cancer Center
2010	Faculty Search Committee for Chair, Department of Pathology and Laboratory Medicine
2010-2011	Chair, Review Committee Department of Radiation Oncology
2011-2012	Faculty Search Committee for Chair, Department of Radiology

2011-2012	Chair, Faculty Search Committee for Director, Penn Institute for Immunology
2015-2016	Faculty Search Committee for Chair, Department of Biophysics and Biochemistry
2016-2017	Chair, Faculty Search Committee for Chair, Department of Systems Pharmacology and Translational Therapeutics
2016	President's Consultative Review Committee on the Reappointment of the Dean of the Perelman School of Medicine
2016-	APAC, University of Pennsylvania
2019-	Celgene, Joint Advisory Committee (Ben Garcia)
2020-	Undergraduate Medical Education Committee Perelman School of Medicine, University of Pennsylvania
2020-	Patent Policy Advisory Working Group University of Pennsylvania

Major Teaching and Clinical Responsibilities at the University of Pennsylvania :

1. Attending Physician, Hospital of the University of Pennsylvania (1992-present)
   Endocrine consult service - one month per year (1996-2005)
2. Supervision of graduate students performing thesis research
   Heather Perry Gardner (1996-00)
   Celina D'Cruz (1996-00)
   Stephen Master (Combined Degree Program) (1995-01)
   Gerald Wertheim (Combined Degree Program) (1998-03)
   Susan Moody (Combined Degree Program) (1999-03)
   Robert Boxer (Combined Degree Program) (1999-03)
   Christopher Sarkisian (1998–04)
   Douglas Stairs (1998–04)
   Thomas Yang (1999-05)
   Collin Blakely (Combined Degree Program) (2002-05)
   Joanne Jang (Combined Degree Program) (2002-06)
   Zhandong Liu (2005-10)
   Dania Daye (Combined Degree Program) (2010-2012)
   Jason Jung (2008-13)
   Samantha Eberle (2007-13)
   Daniel Abravanel (Combined Degree Program) (2009-2013)
   Ania Payne (2010-2014)
   Jason Ruth (2010-2014)
   Lauren Smith Pferdehirt (2010-2015)
   Sam Getchell (2010-2016)
   Matthew Paul (2015-2020)
   Takashi Nakamura (2016-)
   Katherine Huang (2018-)
   Saisai Chen (Combined Degree Program) (2018-)
   Brian Benz (2019-)
   Emily Shea (Combined Degree Program) (2021-)
3. Supervision of postdoctoral trainees
   Man Wang, Ph.D. (1995-96)
   Edward Gunther, M.D. (1997-98; 1999-02)

L. Julie Huber, Ph.D. (1997-01)
Eunkyung A. Kauh, M.D., Ph.D. (1999-05)
Charles Bailey, M.D., Ph.D. (2002-07)
Min Wang, Ph.D. (2002-07)
Xiaoping Yang, Ph.D. (2003-07)
Suzanne Bakewell, Ph.D. (2005-09)
James Alvarez, Ph.D. (2005-09)
Chien-Chung Chen, Ph.D. (2004-09)
Elizabeth Yeh, Ph.D. (2006-13)
Yi Feng, Ph.D. (2006-14)
Ann Vernon-Grey, Ph.D. (2006-14)
Heather Martin, Ph.D. (2007-18)
Beth Chislock, Ph.D. (2014-19)
Brett Ecker, M.D. (2016-18)
Francesco Marino, Ph.D. (2017-20)
Matias Escobar, Ph.D. (2017-20)
Amulya Sreekumar, Ph.D. (2017-)
Adetutu Egunsola, Ph.D. (2018-20)

4. Supervision of undergraduate trainees
   Alexander Golant (2001-02)
   Lilangi Ediwickirema (2002-06)
   Srujan Peddapaidi (2005-09)
   Kristi Chakrabarti (2006-10)
   Sanjee Baksh (2012-14)
   Gabriella Puig (2013-16)
   Joseph Kim (2015-17)
   Aaron Solomon (2016-17)
   Alice Zhou (2018-20)
   John Koga (2019-)
   Michelle Lu (2019-)
5. Supervision of masters students
   Alexander Stoddard (2000-01)
   Congzhou Liu (2004-07)
   Elise Giantomaso (2008-09)
6. Supervision of graduate students in laboratory rotations
   1-2 students per semester
7. Supervision of undergraduate students in laboratory rotations
   1-2 students per year
8. Thesis committee member:
   Dongsheng Duan (Ph.D., 1997)
   Hongbing Zhang (Ph.D., 1998)
   Matthew Waterman (Ph.D., 1998)
   Hongtao Zhang (Ph.D., 1999)
   Christopher Wong (Ph.D., 2001)
   Meredith Unger (Ph.D., 2002; Chair)
   Oana Tomescu (Ph.D., 2002)
   Joanna Sax (Ph.D., 2003)
   Michael Keeley (Ph.D., 2005)
   Andrew Gladden (Ph.D., 2005)

Phillip Le (Ph.D., 2005)
Rebekah O'Donnell (Ph.D., 2005)
Jagruti Patel (Ph.D., 2006)
Monica Buzzai (Chair; Ph.D., 2006)
Dara Ditsworth (Chair, Ph.D., 2008)
Karen Urtishak (Ph.D., 2009)
David Schoppy (Ph.D., 2011)
Derek Oldridge (Chair; Ph.D., 2016)
William Rothwell (Chair; Ph.D., 2017)
Emily Fernandez Garcia (Chair;)
Nicholas Perkins (Ph.D., 2020)
Chi-Yun Wu (Ph.D.,)
Austin Pantel (M.S.T.R., 2020)

9. Preliminary examination committee member
Holly Kurzawa (1995)
Christopher Wong (1996)
Praveen Raju (1996)
Gregory Heuer (1998)
Hongbing Zhang (1996)
Michael Gee (1998)
Elizabeth Higbee (2014)
Heide Norton (2015)
Jessica Hsu (2016)
Sofya Osharovich (2017)
Hannah Richter (2017)
Alex Chan (2020)
Hau Truong (2021)

10. Continuing Medical Education
Sacred Heart Hospital, Allentown PA – 1995
Women's Health Research Conference – 1996, 1997
American College of Physicians, Philadelphia, PA

Teaching Lectures:

1995 Ethics in Biomedical Research (faculty facilitator)
1996 CAMB 605 Mammalian Differentiation and Development
Course co-director (12 classes)
1996 Mammary Development and Breast Cancer Risk
Wistar Institute Cancer Biology Training Course
1997 Molecular Basis of Cancer: Part 1
CAMB 610 Molecular Basis of Gene Therapy (course co-director)
1997 Molecular Basis of Cancer: Part 2
CAMB 610 Molecular Basis of Gene Therapy (course co-director)
1997 Tumor Suppressor Gene Strategies for Gene Therapy
CAMB 610 Molecular Basis of Gene Therapy (course co-director)
1997 Strategies for Cancer Gene Therapy
CAMB 610 Molecular Basis of Gene Therapy (course co-director)
1997 The Molecular Basis of Epidemiological Observations
Center for Clinical Epidemiology Training Course

1998 Ethics in Biomedical Research (faculty facilitator)
1998 Anatomy, Development and Physiology of the Breast
Module 1: Brain, Behavior, Endocrine/Reproduction
1998 Molecular Basis of Cancer: Part 1
CAMB 610 Molecular Basis of Gene Therapy (course co-director)
1998 Molecular Basis of Cancer: Part 2
CAMB 610 Molecular Basis of Gene Therapy (course co-director)
1998 Tumor Suppressor Gene strategies for Gene Therapy
CAMB 610 Molecular Basis of Gene Therapy (course co-director)
1998 Strategies for Cancer Gene Therapy
CAMB 610 Molecular Basis of Gene Therapy (course co-director)
1999 Anatomy, Development and Physiology of the Breast
Module 1: Brain, Behavior, Endocrine/Reproduction
1999 The Molecular Basis of Epidemiological Observations
Center for Clinical Epidemiology Training Course
1999 Molecular Basis of Cancer: Part 1
CAMB 610 Molecular Basis of Gene Therapy (course co-director)
1999 Molecular Basis of Cancer: Part 2
CAMB 610 Molecular Basis of Gene Therapy (course co-director)
1999 Tumor Suppressor Gene strategies for Gene Therapy
CAMB 610 Molecular Basis of Gene Therapy (course co-director)
1999 Strategies for Cancer Gene Therapy
CAMB 610 Molecular Basis of Gene Therapy (course co-director)
1999 Strategies for Cancer Gene Therapy
CAMB 610 Molecular Basis of Gene Therapy (course co-director)
1999 Development and Cancer Susceptibility
CAMB 620 Developmental Biology
2000 Anatomy, Development and Physiology of the Breast
Module 1: Brain, Behavior, Endocrine/Reproduction
2000 Molecular Basis of Cancer: Part 1
CAMB 610 Molecular Basis of Gene Therapy
2000 Molecular Basis of Cancer: Part 2
CAMB 610 Molecular Basis of Gene Therapy
2000 Strategies for Cancer Gene Therapy
CAMB 610 Molecular Basis of Gene Therapy
2001 Breast Cancer Genetics and Genomics
CAMB 512 Cancer Genetics
2001 Molecular Basis of Cancer: Part 1
CAMB 610 Molecular Basis of Gene Therapy
2001 Molecular Basis of Cancer: Part 2
CAMB 610 Molecular Basis of Gene Therapy
2001 Strategies for Cancer Gene Therapy
CAMB 610 Molecular Basis of Gene Therapy
2001 Strategies for Cancer Gene Therapy
CAMB 610 Molecular Basis of Gene Therapy
2002 Mammary Development and Cancer: Part 1
CAMB 665 Cancer and Development
2002 Mammary Development and Cancer: Part 2
CAMB 665 Cancer and Development

2002 Mammary Development and Cancer: Part 3
CAMB 665 Cancer and Development
2002 Breast Cancer
CAMB 512 Cancer Genetics
2002 Cancer Genomics
CAMB 512 Cancer Genetics
2002 Molecular Basis of Cancer: Part 1
CAMB 610 Molecular Basis of Gene Therapy
2002 Molecular Basis of Cancer: Part 2
CAMB 610 Molecular Basis of Gene Therapy
2002 Strategies for Cancer Gene Therapy
CAMB 610 Molecular Basis of Gene Therapy
2002 Strategies for Cancer Gene Therapy
CAMB 610 Molecular Basis of Gene Therapy
2003 Mammary Development and Cancer: Part 1
CAMB 665 Cancer and Development
2003 Mammary Development and Cancer: Part 2
CAMB 665 Cancer and Development
2003 Mammary Development and Cancer: Part 3
CAMB 665 Cancer and Development
2004 Molecular Basis of Cancer: Part 1
CAMB 610 Molecular Basis of Gene Therapy
2004 Molecular Basis of Cancer: Part 2
CAMB 610 Molecular Basis of Gene Therapy
2004 Oncogene Addiction and Targeted Therapies
CAMB 542 Topics in Molecular Medicine
2005 Molecular Basis of Cancer: Part 1
CAMB 610 Molecular Basis of Gene Therapy
2005 Molecular Basis of Cancer: Part 2
CAMB 610 Molecular Basis of Gene Therapy
2005 CML, BCR-ABL, and the Philadelphia Chromosome
FRO 514 Frontiers in Cancer Research
2005 Kinase Inhibition: A Paradigm for Molecularly Targeted Therapies
FRO 514 Frontiers in Cancer Research
2006 Breast Cancer Genetics and Genomics: Part 1
CAMB 512 Cancer Genetics
2006 Breast Cancer Genetics and Genomics: Part 2
CAMB 512 Cancer Genetics
2006 Molecular Basis of Cancer: Part 1
CAMB 610 Molecular Basis of Gene Therapy
2006 Molecular Basis of Cancer: Part 2
CAMB 610 Molecular Basis of Gene Therapy
2006 Oncogene Addiction
FRO 514 Frontiers in Cancer Research (course director)
2006 Molecularly Targeted Therapies
FRO 514 Frontiers in Cancer Research (course director)
2006 Cancer Stem Cells
FRO 514 Frontiers in Cancer Research (course director)
2007 Molecular Basis of Cancer: Part 1

CAMB 610 Molecular Basis of Gene Therapy
2007 Molecular Basis of Cancer: Part 2
CAMB 610 Molecular Basis of Gene Therapy
2007 Oncogene Addiction
FRO 514 Frontiers in Cancer Research (course director)
2007 Molecularly Targeted Therapies
FRO 514 Frontiers in Cancer Research (course director)
2007 Cancer Stem Cells
FRO 514 Frontiers in Cancer Research (course director)
2008 Personalized Medicine, Molecularly Targeted Therapies and Oncogene Addiction
Internal Medicine Core Clerkship
2008 Oncogene Addiction
FRO 514 Frontiers in Cancer Research (course director)
2008 Molecularly Targeted Therapies
FRO 514 Frontiers in Cancer Research (course director)
2008 Cancer Stem Cells
FRO 514 Frontiers in Cancer Research (course director)
2009 Cancer Epidemiology
BIOM 502/Mechanisms of Disease and Therapeutic Intervention
2009 Cancer: Part 1
BIO 015 Biology of Human Disease
2009 Cancer: Part 2
BIO 015 Biology of Human Disease
2009 Cancer: Part 3
BIO 015 Biology of Human Disease
2009 Cancer: Part 4
BIO 015 Biology of Human Disease
2009 Oncogene Addiction
FRO 514 Frontiers in Cancer Research (course director)
2009 Molecularly Targeted Therapies
FRO 514 Frontiers in Cancer Research (course director)
2009 Cancer Stem Cells
FRO 514 Frontiers in Cancer Research (course director)
2010 Cancer Epidemiology
BIOM 502/Mechanisms of Disease and Therapeutic Intervention
2010 Cancer: Part 1
BIO 015 Biology of Human Disease
2010 Cancer: Part 2
BIO 015 Biology of Human Disease
2010 Cancer: Part 3
BIO 015 Biology of Human Disease
2010 Cancer: Part 4
BIO 015 Biology of Human Disease
2010 Oncogene Addiction
FRO 514 Frontiers in Cancer Research (course director)
2010 Molecularly Targeted Therapies
FRO 514 Frontiers in Cancer Research (course director)
2010 Cancer Stem Cells
FRO 514 Frontiers in Cancer Research (course director)

2010 Breast Cancer: Personalized Medicine and Targeted Therapies: Part 1
BIOM 502 Mechanisms of Disease and Clinical Applications
2010 Breast Cancer: Personalized Medicine and Targeted Therapies: Part 2
BIOM 502 Mechanisms of Disease and Clinical Applications
2011 Cancer Epidemiology
BIOM 502/Mechanisms of Disease and Therapeutic Intervention
2011 Cancer: Part 1
BIO 015 Biology of Human Disease
2011 Cancer: Part 2
BIO 015 Biology of Human Disease
2011 Cancer: Part 3
BIO 015 Biology of Human Disease
2011 Cancer: Part 4
BIO 015 Biology of Human Disease
2011 Oncogene Addiction
FRO 514 Frontiers in Cancer Research (course director)
2011 Molecularly Targeted Therapies
FRO 514 Frontiers in Cancer Research (course director)
2011 Cancer Stem Cells
FRO 514 Frontiers in Cancer Research (course director)
2011 Breast Cancer: Personalized Medicine and Targeted Therapies: Part 1
BIOM 502 Mechanisms of Disease and Clinical Applications
2011 Breast Cancer: Personalized Medicine and Targeted Therapies: Part 2
BIOM 502 Mechanisms of Disease and Clinical Applications
2012 Cancer Biology
BIO 121 Molecular Biology of Life
2012 Cancer Epidemiology
BIOM 502/Mechanisms of Disease and Therapeutic Intervention
2012 Cancer: Part 1
BIO 015 Biology of Human Disease
2012 Cancer: Part 2
BIO 015 Biology of Human Disease
2012 Cancer: Part 3
BIO 015 Biology of Human Disease
2012 Cancer: Part 4
BIO 015 Biology of Human Disease
2012 Oncogene Addiction
FRO 514 Frontiers in Cancer Research (course director)
2012 Molecularly Targeted Therapies
FRO 514 Frontiers in Cancer Research (course director)
2012 Cancer Stem Cells
FRO 514 Frontiers in Cancer Research (course director)
2013 Cancer Epidemiology
BIOM 502/Mechanisms of Disease and Therapeutic Intervention
2013 Cancer: Part 1
BIO 015 Biology of Human Disease
2013 Cancer: Part 2
BIO 015 Biology of Human Disease
2013 Cancer: Part 3

BIO 015 Biology of Human Disease
2013 Cancer: Part 4
BIO 015 Biology of Human Disease
2013 Cancer: Part 5
BIO 015 Biology of Human Disease
2013 Oncogene Addiction
FRO 514 Frontiers in Cancer Research (course director)
2013 Molecularly Targeted Therapies
FRO 514 Frontiers in Cancer Research (course director)
2013 Cancer Stem Cells
FRO 514 Frontiers in Cancer Research (course director)
2014 Cancer Epidemiology
BIOM 502/Mechanisms of Disease and Therapeutic Intervention
2014 Cancer: Part 1
BIO 015 Biology of Human Disease
2014 Cancer: Part 2
BIO 015 Biology of Human Disease
2014 Cancer: Part 3
BIO 015 Biology of Human Disease
2014 Cancer: Part 4
BIO 015 Biology of Human Disease
2014 Cancer: Part 5
BIO 015 Biology of Human Disease
2014 Oncogene Addiction
FRO 514 Frontiers in Cancer Research (course director)
2014 Molecularly Targeted Therapies
FRO 514 Frontiers in Cancer Research (course director)
2014 Cancer Stem Cells
FRO 514 Frontiers in Cancer Research (course director)
2015 Cancer Epidemiology
Mechanisms of Disease and Therapeutic Intervention
2015 Cancer: Part 1
BIO 015 Biology of Human Disease
2015 Cancer: Part 2
BIO 015 Biology of Human Disease
2015 Cancer: Part 3
BIO 015 Biology of Human Disease
2015 Cancer: Part 4
BIO 015 Biology of Human Disease
2015 Cancer: Part 5
BIO 015 Biology of Human Disease
2015 Cancer Epidemiology
Medical Student Core Curriculum – Module 1
2015 Cancer Biology, Treatment and Natural History
Medical Student Core Curriculum – Module 1
2015 CAMB 512: Cancer Biology and Genetics
Metastasis
2016 Cancer: Part 1
BIO 015 Biology of Human Disease

2016 Cancer: Part 2
BIO 015 Biology of Human Disease
2016 Cancer: Part 3
BIO 015 Biology of Human Disease
2016 Cancer: Part 4
BIO 015 Biology of Human Disease
2016 Cancer: Part 5
BIO 015 Biology of Human Disease
2016 Cancer Epidemiology
Medical Student Core Curriculum – Module 1
2016 Cancer Biology, Treatment and Natural History
Medical Student Core Curriculum – Module 1
2017 Cancer: Part 1
BIO 015 Biology of Human Disease
2017 Cancer: Part 2
BIO 015 Biology of Human Disease
2017 Cancer: Part 3
BIO 015 Biology of Human Disease
2017 Cancer: Part 4
BIO 015 Biology of Human Disease
2017 Cancer: Part 5
BIO 015 Biology of Human Disease
2017 Cancer Epidemiology
Medical Student Core Curriculum – Module 1
2017 Cancer Biology, Treatment and Natural History
Medical Student Core Curriculum – Module 1
2018 CAMB 512: Cancer Biology and Genetics
Metastasis
2018 Cancer Epidemiology
Medical Student Core Curriculum – Module 1
2018 Cancer Biology, Treatment and Natural History
Medical Student Core Curriculum – Module 1
2019 Tissue Growth and Renewal
Medical Student Core Curriculum – Module 1
2019 Cell Cycle Control
Medical Student Core Curriculum – Module 1
2019 Director, Cancer Biology Module
Medical Student Core Curriculum – Module 1
2019 Cancer Epidemiology
Medical Student Core Curriculum – Module 1
2019 Cancer Biology, Treatment and Natural History
Medical Student Core Curriculum – Module 1
2019 Cancer Cell Hallmarks, Heterogeneity and Metastasis
Medical Student Core Curriculum – Module 1
2019 Oncogenic Signaling Pathways: RAS and PI3K
Medical Student Core Curriculum – Module 1
2019 Cancer Cell Metabolism
Medical Student Core Curriculum – Module 1
2019 Molecular Basis of Targeted Therapies

Medical Student Core Curriculum – Module 1
2019 Other Hallmarks of Cancer and Role of Stromal Cells
Medical Student Core Curriculum – Module 1
2019 Cancer Biology, Treatment and Natural History
Medical Student Core Curriculum – Module 1
2020 Tissue Growth and Renewal
Medical Student Core Curriculum – Module 1
2020 Cell Cycle Control
Medical Student Core Curriculum – Module 1
2020 Director, Cancer Biology Module
Medical Student Core Curriculum – Module 1
2020 Cancer Epidemiology
Medical Student Core Curriculum – Module 1
2020 Cancer Biology, Treatment and Natural History
Medical Student Core Curriculum – Module 1
2020 Cancer Cell Hallmarks, Heterogeneity and Metastasis
Medical Student Core Curriculum – Module 1
2020 Oncogenic Signaling Pathways: RAS and PI3K
Medical Student Core Curriculum – Module 1
2020 Cancer Cell Metabolism
Medical Student Core Curriculum – Module 1
2020 Molecular Basis of Targeted Therapies
Medical Student Core Curriculum – Module 1
2020 Other Hallmarks of Cancer and Role of Stromal Cells
Medical Student Core Curriculum – Module 1

Lectures by Invitation (past 9 years):

August, 2011 "Mechanisms of Breast Cancer Recurrence"
DOD Era of Hope, Orlando, FL
August, 2011 "Minimal Residual Disease and Mammary Stem Cells"
DOD Era of Hope, Orlando, FL
October, 2011 "Rewriting Cancer History"
TEDx Penn 2011, Philadelphia, PA
November, 2011 "Probing Tumor Dormancy and Recurrence"
American Physician Scientists Association 2011 Regional Meeting
Philadelphia, PA
November, 2012 "Modeling Breast Cancer Progression" Dana Farber Cancer Institute
Harvard Medical School, Boston, MA
December, 2012 "Mechanisms of Breast Cancer Dormancy and Recurrence"
San Antonio Breast Cancer Symposium, San Antonio, CA
December, 2012 "Molecular Imaging to Characterize Breast Cancer Models"
San Antonio Breast Cancer Symposium, San Antonio, CA
January, 2013 "Pathways in Tumor Dormancy and Recurrence" AACR Tumor Invasion and Metastasis Special Conference, San Diego, CA
February, 2013 "Mechanisms of Breast Cancer Recurrence" UMDNJ, Newark, NJ
March, 2013 "Mechanisms of Breast Cancer Progression" Duke University, Durham, NC

March, 2013	"Pathways in Tumor Dormancy and Recurrence" Medical University of South Carolina, Charleston, SC
April, 2013	"Mechanisms of Tumor Dormancy and Recurrence" AACR Annual Meeting, Washington, DC
June, 2013	"Breast Cancer Recurrence via Escape from Par-4-dependent Multinucleation and Arrest" Mammary Gland Biology Gordon Research Conference, Stowe, VT
September, 2013	"Dormant Tumor Cell Survival and Recurrence" International Symposium on Minimal Residual Disease, Paris, France
October, 2013	"Mechanisms of Breast Cancer Dormancy and Recurrence" AACR Advances in Breast Cancer Research, San Diego, CA
October, 2013	"Minimal Residual Disease and Breast Cancer Recurrence" Breast Cancer Research Foundation, New York, NY
November, 2013	"Mechanisms of Tumor Dormancy and Recurrence" Massachusetts General Hospital, Harvard Medical School, Boston, MA
December, 2013	"Basic Science: The Year in Review" San Antonio Breast Cancer Symposium, San Antonio, CA
February, 2014	"Tumor Initiating Cells and Minimal Residual Disease" Keystone Symposium on Stem Cells and Cancer, Banff, Alberta
June, 2014	"Probing Tumor Dormancy and Recurrence" NCI Mouse Models for Human Cancers Consortium, Gaithersburg, MD
November, 2014	"Tumor Dormancy and Recurrence: Novel Biology and Therapeutic Opportunities" GlaxoSmithKline Delaware Valley Biology Day, Collegeville, PA
November, 2014	"Tumor Dormancy and Breast Cancer Recurrence" Vanderbilt-Ingram Cancer Center, Nashville, TN
January, 2015	"Tumor Dormancy and Recurrence" Breast Cancer Symposium, George Town, Cayman Islands
April, 2015	"Tumor Dormancy and Recurrence" AACR Annual Meeting, Philadelphia, PA
August, 2015	Keynote speaker 11th Annual Breast Cancer Research and Education Program, Baylor College of Medicine, Montgomery, TX
October, 2015	"Tumor Dormancy and Recurrence" Fourth International AACR Conference on Frontiers in Basic Cancer Research, Philadelphia, PA
March, 2016	"Impact of Obesity, Exercise and Caloric Restriction on Breast Cancer Recurrence in Mice" Transdisciplinary Research on Energetics and Cancer, National Cancer Institute, Rockville, MD
April, 2016	"Tumor Dormancy and Recurrence: Novel Biology and Therapeutic Opportunities" MD Anderson Cancer Center, Houston, TX
November, 2016	"Breast Cancer Recurrence: When the Dragon Awakes" 2016 Jensen Symposium on Breast Cancer University of Cincinnati, Cincinnati, OH
June, 2017	"Tumor Dormancy as a Window to Prevent Metastatic Recurrence" Gordon Research Conference on Mammary Gland Biology Stowe, VT
October, 2017	"Tumor Dormancy and Breast Cancer Recurrence" University of Pittsburgh, Pittsburgh, PA
October, 2017	"Tumor Dormancy and Breast Cancer Recurrence" Symposium on Biology of Cancer: Microenvironment and Metastasis"

	Cold Spring Harbor Laboratory, Cold Spring Harbor, NY
October, 2017	"Breast Cancer Recurrence: Slaying the Sleeping Dragon" Carol M. Baldwin Distinguished Lecture SUNY Upstate Medical University, Syracuse, NY
October, 2017	"Breast Cancer Recurrence: When the Dragon Awakes" Symposium on Metastatic Breast Cancer Jayne Koskinas Ted Giovanis Foundation for Health and Policy Bethesda, MD
May, 2018	"Targeting Tumor Dormancy to Prevent Breast Cancer Recurrence" 11th International Symposium on Minimal Residual Cancer Montpelier, France
November, 2018	"Tumor Dormancy and Metastatic Breast Cancer Recurrence" 5th Annual Metastatic Breast Cancer Conference Johns Hopkins University, Baltimore, MD
December, 2018	"Tumor Dormancy and Cancer Recurrence" Salk Institute Cancer Symposium Salk Institute, La Jolla, CA
December, 2018	"Tumor Dormancy and Late Recurrence" San Antonio Breast Cancer Symposium 2018 San Antonio, TX
April, 2019	"Therapeutic Opportunities: Minimal Residual Disease, Tumor Dormancy and Cancer Recurrence" AACR Annual Meeting, Atlanta, GA
June, 2019	"Minimal Residual Disease, Tumor Dormancy and Cancer Recurrence: Therapeutic Opportunities" Keynote Speaker, Annual Research Symposium, Karmanos Cancer Institute, Wayne State University, Detroit, MI
July, 2019	"Tumor Dormancy and Metastatic Breast Cancer Recurrence" 34th Aspen Cancer Conference, Aspen, CO
October, 2019	"Tumor Cell Dormancy and Breast Cancer Recurrence" British Association for Cancer Research, Newcastle Gateshead, UK
January, 2020	"Tumor Cell Dormancy, Minimal Residual Disease and Breast Cancer Recurrence", Department of Medicine, Department Pediatrics, Division of Hematology/Oncology, Herman B. Wells Center for Pediatric Research, and Simon Cancer Center, Indiana University, Indianapolis, IN
January, 2020	"When the Dragon Awakes: Preventing Breast Cancer Recurrence" Grand Rounds, Simon Cancer Center, Indiana University, Indianapolis, IN
March, 2020	"Minimal Residual Disease and Breast Cancer Recurrence" Cold Spring Harbor Laboratory, Cold Spring Harbor, NY [cancelled due to COVID-19]
July, 2020	"Detecting and Targeting Dormant Tumor Cells to Prevent Death from Recurrent Cancer" Emerson Collective Virtual Symposium
October, 2020	"Changing the Paradigm to Prevent Breast Cancer Recurrence" Yale Alumni Health Network Virtual Symposium
December, 2020	"Dormancy" San Antonio Breast Cancer Symposium Educational Session

Organizing Roles in Scientific Meetings:

April, 2001	Co-Chair, NCI Workshop on BRCA1 Function National Cancer Institute, Bethesda, MD
October, 2003	Conference Co-Chair, AACR Special Conference in Cancer Research: Advances in Breast Cancer Research, Huntington Beach, CA
June, 2004	Chair, Scientific Symposium: "Preclinical Models and Molecular Therapeutics in Cancer" - 2004 ASCO Annual Meeting, New Orleans, LA
April, 2005	"Stem Cells, Metastasis, and Residual Disease: Integrating New Findings in Breast Cancer Research" - Symposium Co-Chair, AACR 96th Annual Meeting, Anaheim, CA
September, 2005	Conference Co-Chair, AACR Special Conference in Cancer Research: Advances in Breast Cancer Research: Genetics, Biology, and Clinical Applications, La Jolla, CA
April, 2006	Program Committee, Chair: Animal Models Subsection AACR 97th Annual Meeting, Washington, DC
October, 2007	Conference Co-Chair, AACR Special Conference in Cancer Research: Advances in Breast Cancer Research: Genetics, Biology, and Clinical Applications, San Diego, CA
December, 2008	SABCS Program Planning Committee, 2008 AACR-CRTC San Antonio Breast Cancer Meeting
October, 2009	Conference Co-Chair, AACR Special Conference in Cancer Research: Advances in Breast Cancer Research: Genetics, Biology, and Clinical Applications, San Diego, CA
November, 2012	NCI Breast Cancer Models Summit, University of Pennsylvania, Philadelphia, PA

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Research Publications, peer-reviewed reviews

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Contribution to peer-reviewed clinical research publications, participation cited but not by authorship:

[none]

Research Publications, non-peer reviewed:

[none]

Abstracts:

Editorials, Reviews, Chapters, including participation in committee reports (print or other media):

Chodosh LA. Science and the Secret of Life. *Prism* 2:13-18, 1984.

Chodosh LA. Mobility shift DNA-binding assay. In *Current Protocols in Molecular Biology*. Ausubel, F.M. et al., eds. pp. 12.2.1-12.2.10. John Wiley & Sons, 1988.

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Books:

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Alternative Media:

[none]

Patents:

Chodosh, LA: U.S. entitled: "Hormonally Up-Regulated, Neu-Tumor-Associated Kinase". Patent Nos.: 7,119,185 and 7,368,113.

Chodosh, LA: U.S. entitled: "Pregnancy, Up-Regulated Non-Ubiquitous CaM Kinase". Patent Nos.: 7,041,495 and 7,741,111.

Extramural Funding:

ACTIVE

2 R01 CA098371 (Chodosh, PI) 4/18/03 – 2/28/22
NIH/NCI $207,500 annual direct costs
In vivo oncogene-induced tumorigenesis and escape

2 R01 CA148774 (Chodosh, PI) 09/22/10-11/30/22
NIH/NCI $228,750 annual direct costs
Survival and recurrence of dormant cancer cells

2 R01 CA143296 (Chodosh, PI) 06/30/10-05/31/23
NIH/NCI $237,500 annual direct costs
Minimal residual disease and mechanisms of breast cancer recurrence

R01 CA208273 (Chodosh, PI; DeMichele, PI) 12/13/16-11/30/21
NIH/NCI $294,863 annual direct costs
Secondary prevention through surveillance and intervention

R01 CA223816 (Chodosh, PI; Kontos, PI) 07/03/18-5/31/23
NIH/NCI $282,418 annual direct costs
Radiogenomic biomarkers of breast cancer recurrence

W81XWH-17-1-0594 (Chodosh PI) 9/30/17-8/31/20
DOD $264,498 annual direct costs
Dynamic response of disseminated tumor cells and circulating tumor markers to targeted adjuvant therapy

BCRF-16-026 (Chodosh, PI) 10/01/04-9/30/21
Breast Cancer Research Foundation $145,833 annual direct costs
Pathways in breast cancer progression

W81XWH-20-1-0008 (Chodosh PI; DeMichele Partnering PI) 1/15/20-1/14/22
DOD $652,188 annual direct costs
Detecting and defining residual tumor cell subsets to enable recurrence prevention in early stage breast cancer patients

P30 CA016520 (Vonderheide) 12/01/10-11/30/20
NIH/NCI $30,890
University of Pennsylvania Cancer Center Core Grant

CHODOSH

EXHIBIT B

GT GreenbergTraurig

In re: Valsartan, Losartan, and Irbesartan Products Liability Litigation
Case No. 19-2875

LEWIS A. CHODOSH, M.D., PH.D.
AMENDED LIST OF MATERIALS CONSIDERED
SEPTEMBER 24, 2021

MATERIALS CONSIDERED	BATES NOS.
MDL PLEADINGS AND GENERAL DOCUMENTS	
Am. Master Personal Injury Complaint	N/A
Am. Master Medical Monitoring Complaint	N/A
2021.02.11 Letter from Lori G. Cohen to Judge Vanaskie	N/A
2021.02.11 Letter from Adam Slater Providing an Overview	N/A
Am. Master Economic Loss Complaint	N/A
REPORTS AND DISCLOSURES	
2021.07.04 Dr. Mahyar Etiminan Report • CV	N/A
2021.07.06 Dr. Stephen Hecht Report • CV • List of Documents Reviewed • Literature Referenced	N/A
2021.07.06 Dr. Stephen Lagana Report • CV	N/A
2021.07.07 Dr. David Madigan Madigan Report • CV	N/A
2021.07.06 Dr. Dipak Panigrahy Report • CV	N/A
2021.05.18 Dr. Nagi Kumar Report • CV	N/A
2021.05.30 Dr. Steven Bird Report • CV • Deposition Disclosure	N/A
2021.08.02 – Report of Michael Bottorff	N/A
2021.08.02 – Report of Janice Britt	N/A
2021.08.02 – Report of Daniel Catenacci	N/A
2021.08.02 – Report of Lewis Chodosh	N/A
2021.08.02 – Report of Jon Fryzek	N/A
2021.08.02 – Report of John Gibb	N/A
2021.08.02 – Report of George Johnson	N/A
2021.08.02 – Report of Lee-Jen Wei	N/A

WRITTEN DISCOVERY	
Plaintiff's Disclosure of Cancer Types	N/A
TEVA DOCUMENTS	
2018.07.06 Teva Health Hazard Assessment re Valsartan	TEVA-MDL2875-00274341
2018.07.06 Teva Health Hazard Assessment re Valsartan/HCTZ	TEVA-MDL2875-00274351
2018.07.10 Health Hazard Assessment of Amlodipine Valsartan	TEVA-MDL2875-00680243
2018.07.10 Health Hazard Assessment of Amlodipine Valsartan HCTZ	TEVA-MDL2875-00680244
2018.06.29 Teva Toxicological Assessment of NDMA impurity in valsartan by Dr. Nudelman	TEVA-MDL2875-00274358
2018.11.12 Tox Assessment for NDEA in Valsartan by Dr. Nudelman	TEVA-MDL-00953115
2019.03.13 Tox Assessment for NDMA and NDEA in Sartan Drugs in Parellel	TEVA-MDL2875-00773542
2019.07.03 Teva Risk Assessment Report for Valsartan Huahai	TEVA-MDL-00693424
2019.07.03 Teva Risk Assessment Report for Valsartan Mylan	TEVA-MDL-00693422
2019.07.18 Teva Valsartan Analytical Drug Substance & Drug Product Testing Results	TEVA-MDL-0063060
ZHP root cause	TEVA-MDL2875-00783229
Mylan root cause	TEVA-MDL2875-00019995
CBE-30 for ANDA 091519 – Valsartan/HCTZ w/ ZHP API	TEVA-MDL2875-00001886
CBE-30 for ANDA 090642 – Valsartan w/ ZHP API	TEVA-MDL2875-00013107
sANDA Approval by FDA for ANDA 091519	TEVA-MDL2875-00133642
sANDA Approval by FDA for ANDA 090642	TEVA-MDL2875-00354034
Valsartan sales	TEVA-MDL2875-00019951
Valsartan sales	TEVA-MDL2875-00019954
Email with test results	TEVA-MDL2875-00546489
Response to FDA Request for Information (RFI) for Valsartan (Jan 30, 2019)	TEVA-MDL2875-00546490
Testing result of NDMA in valsartan	TEVA-MDL2875-00546493
Balkanpharma Oupnitsa results for NOMA content in Valsartan API, manufactured by Zhejiang Huahai Co.,Ltd	TEVA-MDL2875-00546494
Balkanpharma Oupnitsa results for NOMA content in Valsartan API, manufactured by Zhejiang Huahai Co.,Ltd	TEVA-MDL2875-00546495
Miscellaneous Study Report	TEVA-MDL2875-00546496
Bafkanpharma Dupnitsa results for NOMA content in Valsartan tabfets and Valsartan/HCT tablets	TEVA-MDL2875-00546511

FDA/REGULATORY GUIDANCES AND DOCUMENTS	
Publicly Available FDA Documents	
2018.07.13 FDA Announces Voluntary Recall, FDA News Release	N/A
2018.07.17 Teva Issues Voluntary Recall	N/A
2018.07.18 Recalled US Valsartan Labels	N/A
2018.08.30 FDA Statement on Ongoing Investigation into Valsartan Impurities	N/A
2018.11.27 Teva Announces Voluntary Recall of All Amlodipine	N/A
2019.04.04 FDA Statement – Update on Recall	N/A
2019.04.15 Laboratory analysis of valsartan products	N/A
2019.06.13 Valisure Citizens Petition	N/A
2020.10.02 FDA Overview of Guidance for Industry	N/A
2020.12.04 - Laboratory analysis of valsartan products - FDA	N/A
2021 - Laboratory analysis of valsartan products, https://www.fda.gov/drugs/drug-safety-and-availability/laboratory-analysis-valsartan-products	N/A
2021 - FDA. Valsartan package insert, https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021283s033lbl.pdf	N/A
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DEPOSITION TRANSCRIPTS (WITH EXHIBITS)	
Teva Witnesses	
Raphael Nudelman – 04.08.2021 - Transcript	N/A
79 - Notice of Deposition	N/A
80 - Response to Plaintiffs' Document Requests	N/A
81 - Resumé Raphael Nudelman, Ph.D., ERT	TEVA-MDL2875-DEPS-000019-24
82 - LinkedIn Raphael Nudelman, Ph.D., ERT	TEVA-MDL2875-DEPS-000025-26
83 - No Exhibit	No Exhibit
84 - No Exhibit	No Exhibit
85 - Audit Report On ZHP (Chuannan Site) 9/2/11	TEVA-MDL2875-00051288
86 - No Exhibit	No Exhibit
87 - Auditing of API Manufacturers 3/27/12	TEVA-MDL2875-00102747
88 - E-mail, 7/4/12 Subject, Genotoxicity Evaluation for Valsartan (Azide Route)	TEVA-MDL2875-00539802
89 - Computational Toxicology Report for Valsartan Reagents and Intermediates 7/19/12	TEVA-MDL2875-00259857
90 - E-mail Thread 8/1/12 Subject, Acetaldehyde Toxicity	TEVA-MDL2875-00514864-66
91 - No Exhibit	No Exhibit
92 - No Exhibit	No Exhibit
93 - E-mail Thread 3/30/14 Subject, Amlodipine Besilate	TEVA-MDL2875-00158436-39
94 - Caspofungin 50-70 mg Powder for Concentrate For Solution for Infusion 3.2.P.2	TEVA-MDL2875-00917440-19
95 - Computational Mutagenicity Report For Potential Impurity In Valsartan 10/14/15	TEVA-MDL2875-00259986-87
96 - E-mail Thread 6/15/16 Subject, Toxicology of Hydrolyzed Calpronium Chloride	TEVA-MDL2875-00158463-69
97 - No Exhibit	No Exhibit

98 - E-mail Thread 12/19/17 Subject, Valsartan Proposal for API Specifications Revision US	TEVA-MDL2875-00082321-24
99 - Computational Mutagenicity and Control Recommendations For Potential Impurities In Valsartan	TEVA-MDL2875-00158698-05
100 - Quality Risk Management for Cross Contamination Control	TEVA-MDL2875-00260122
101 - E-mail Thread 6/28/18 Urgent and Important Genotoxic Impurity Notification	TEVA-MDL2875-00056559-61
102 - Request for Safety Assessment of NDMA for Valsartan Dose 1x Daily for 320mg, 160mg, 80mg (June 28, 2018)	TEVA-MDL2875-00425812-14
103 - Toxicological Assessment for NDMA In Valsartan Drug Substance 6/29/18	TEVA-MDL2875-00158529
104 - No Exhibit	No Exhibit
105 - E-mail Thread 7/3/18 Subject, Urgent Valsartan Safety Assessment Request	TEVA-MDL2875-00158519-22
106 - E-mail Thread 7/4/18 Subject Valsartan Urgent	TEVA-MDL2875-00056924-29
107 - E-mail Thread 7/4/18 Subject, Valsartan Urgent	TEVA-MDL2875-00514896-02
108 - E-mail Thread 7/4/18 Subject, Valsartan Urgent	TEVA-MDL2875-00020609-18
109 - E-mail Thread 7/5/18 Subject, Valsartan Urgent	TEVA-MDL2875-00158540-41
110 - E-mail Thread 7/5/18 Subject, Valsartan Urgent	TEVA-MDL2875-00495085
111 - E-mail Thread 7/5/18 Subject, Valsartan HHA draft V3 for Review	TEVA-MDL2875-00057083-85
112 - No Exhibit	No Exhibit
113 - No Exhibit	No Exhibit
114 - Draft HHA Valsartan Tablets 40, 80, 160, 320 Multiple Lots	TEVA-MDL2875-00057086-94
115 - No Exhibit	No Exhibit
116 - E-mail Thread 7/12/18 Subject, Valsartan	TEVA-MDL2875-00158544
117 - E-mail Thread 7/13/18 Subject, Valsartan Request from Hong Kong	TEVA-MDL2875-00540426-30
118 - E-mail Thread 7/13/18 Subject, EDQM Valsartan Provisional Limit Potential Impact on HHAs	TEVA-MDL2875-00021077-78
119 - Certification of Substances Department 8/10/18 Request for Information Relating to EU Referral Article 31 of Directive 2001/83/EC	N/A
120 - No Exhibit	No Exhibit
121 - E-mail Thread 9/6/18 Subject, Draft Valsartan Letter	TEVA-MDL2875-00552854-59
121A - NDMA Acceptable Limit (Handwritten Document From Plaintiff's Counsel Watt)	N/A
122 - E-mail Thread 10/22/18 Subject, NDMA & NDEA Limits	TEVA-MDL2875-00514942-43
123 - No Exhibit	No Exhibit

124 - E-mail Thread 12/27/18 Subject, Update 26th December 2018 RV Update	TEVA-MDL2875-00540783-88
125 - No Exhibit	No Exhibit
126 - E-mail Thread 3/26/19 Subject, Snodin & Elder Commentary	TEVA-MDL2875-00492386
127 - E-mail Thread 6/27/19 Subject, Request to be An Honorable Keynote Speaker	TEVA-MDL2875-00540844-46
128 - E-mail Thread 8/11/19 Subject, Editor's Spotlight Switzerland	TEVA-MDL2875-00158591-93
129 - Questionnaire for Excipient Nitrosamines Risk Evaluation	TEVA-MDL2875-00158603-09
130 - E-mail Thread 10/23/19 Subject, Ranitidine NDMA Formation	TEVA-MDL2875-00562588-97
131 - No Exhibit	No Exhibit
132 - No Exhibit	No Exhibit
133 - HHA Valsartan Tablets 40, 60,160, 320mg Multiple Lots	TEVA-MDL2875-00274341-49
134 - Toxicological Assessment for NDMA And NDEA in Parallel in Sartan-Drug Substances	TEVA-MDL2875-00773542
Expert Witnesses	
2021.09.16 –Transcript of Dr. Michael Bottorff • Exhibits 1-8	N/A
2021.09.13 –Transcript of Dr. Daniel Catenacci **2021.09.14 – Transcript of Dr. Daniel Catenacci (rough)** • Exhibits 1-12	N/A
2021.08.24 –Transcript of Mayur Etminan • Exhibits 1-30	N/A
2021.08.17 – Transcript of Dr. Steven Hecht • Exhibits 1-32	N/A
2021.08.05 – Transcript of Dr. David Madigan • Exhibits 1-26	N/A
2021.08.13 – Transcript of Dr. Stephen Lagana • Exhibits 1-33	N/A
2021.09.10 and 2021.09.11 – Transcripts of Dr. Dipak Panigrahy • Exhibits 1-29	N/A
2021.09.14 and 2021.09.15 –Transcripts of Lee-Jen Wei • Exhibits 1-15	N/A
BELLWETHER PLAINTIFFS	
Bonmon, Yolanda	

Plaintiff Fact Sheet	
Plaintiff Fact Sheet, 04/28/2021	YBonmon-PFS-000001 – 748
Deposition	
Bonmon, Yolanda – 2021.04.20 – Transcript	N/A
1 – 2021.04.16 Plaintiff Fact Sheet	N/A
2 – 2021.04.16 Signed Declaration of Plaintiff Fact Sheet	N/A
3 – Photograph of Valsartan Bottle	YBonmon-PPR-000319
4 - 2019.06.17 Amended Complaint - Master Personal Injury Complaint	N/A
5 – 2020.07.21 Bonmon Short Form Complaint	N/A
6 – Bonmon Medical Records from Charles K. Embry, MD	YBonmon-CEmbry-000001 – 88
7 – Bonmon Pharmacy Records from Apothecare Pharmacy	YBonmon-ApothPIII-000001 – 13
8 – Bonmon Medical Records from Bluegrass Women's Healthcare	YBonmon-BlueWHC-000001 – 55
9 – Bonmon Medical Records from Central Medical Associates	YBonmon-CMA-000035 – 89
10 – Bonmon Medical Record from UK Healthcare	YBonmon-PPR-000030
11 – Bonmon Medical Records from Central Medical Associates	YBonmon-CMA-000035 – 89
12 – Bonmon Medical Records from Central Medical Associates	YBonmon-CMA-000001 – 34
13 – Bonmon Medical Records from Hardin Memorial Hospital	YBonmon-HMH-MD-000019 – 480
14 – Bonmon Medical Records from Charles K. Embry, MD	YBonmon-CEmbry-000001 – 88
15 – 2021.04.16 Plaintiff Fact Sheet	N/A
16 – Bonmon executed authorization for New Hope Foster Agency	N/A
17 – Bonmon records from New Hope Foster Homes, Inc.	YBonmon-NHFAFC-HR-000001
18 – Bonmon Executed Tax Authorization	N/A
Medical Records	
Plaintiff Produced Records	YBonmon-PPR-000001 – 658
Apothecare Pharmacy III	YBonmon-ApothPIII-000001 – 13
Bluegrass Women's Healthcare	YBonmon-BlueWHC-000001 – 59
Central Medical Associates PLLC	YBonmon-CMA-000001 – 267
Embry Charles, MD	YBonmon-CEmbry-000001 – 88
Hardin Memorial Hospital	YBonmon-HMH-000001 – 521
Laboratory Corporations of America	YBonmon-LCA-000001 – 7
Lincoln Trail Diagnostics	YBonmon-LTD-000001 – 52
Norton Cancer Institute	YBonmon-NCI-000001 – 11
Norton Healthcare	YBonmon-NortonHealthcare-000001 – 559

UK Albert B. Chandler Hospital	YBonmon-UKABCH-000001 – 162
Walgreen Company	YBonmon-WC-000001 – 9
Briones, Joe	
Plaintiff Fact Sheet	
Plaintiff Fact Sheet, 02/02/2021	JBriones-PFS-000001 – 190
Medical Records	
Plaintiff Produced Records	JBriones-PPR-000001 – 441
Citizens Medical Center	JBriones-CMCen-000001 – 407
DeTar Hospital	JBriones-DeTarH-000001 – 436
Envision Pharmacies	JBriones-EnvisionP-000001 – 2
Gastroenterology of Victoria	JBriones-GVictoria-000001 – 7
HEB Pharmacy	JBriones-HEBPharm-000001 – 2
Minocha, Gulshan MD	JBriones-GKMinocha-000001 – 217
Regional Path Assocs	JBriones-RPA-000001 – 2
University of Texas MD Anderson	JBriones-UTMDACC-RD-000001 – 39
University of Texas MD Anderson Cancer Center	JBriones-UTMDACC-000001 – 8520
Dawson, Nellie	
Plaintiff Fact Sheet	
2020.05.14 Plaintiff Fact Sheet	NDawson-PFS-000092-000180
Medical Records	
Plaintiff-Produced Medical Records	NDawson-PPR-000001-000179
3HC Home Health Hospice Healthcare	NDawson-3HCHH-H-HC-000001-000114
Jordan And Assocs Gastroenterology PA	NDawson-J&AG-000001-000068
Riverdale Family Medicine PA	NDawson-RFM-000001-000332
UNC Health Care System Path Dept	NDawson-UNCHCS-PD-000001-000001
UNC HealthCare System Rad Dept	NDawson-UNCHCS-RD-000001-000001
Dufrene, Lana	
Plaintiff Fact Sheet	
Plaintiff Fact Sheet, 02/10/2021	LDufrene-PFS-000001 – 186
Medical Records	
Plaintiff Produced Records	LDufrene-PPR-000001 – 178
Cardiovascular Institute of the South	LDufrene-CIS-000001 – 183
Lady of the Sea General Hospital	LDufrene-LSGH-000001 – 77
Leonard J. Chabet Medical Center	LDufrene-LJCMC-000001 – 2271
Ochsner Family Doctor Clinic	LDufrene-OFDC-000001 – 193
Racelands Pharmacy	LDufrene-RPE-000001 – 13
Walmart Pharmacy	LDufrene-WMS-000001 – 20
Garcia, Robert	

Plaintiff Fact Sheet	
Plaintiff Fact Sheet, 03/12/2021	RGarcia-PFS-000001 – 283
Medical Records	
Plaintiff Produced Records	RGarcia-PPR-000001 – 434
Baylor St. Lukes Medical Center	RGarcia-BStLMC-000001 – 831
CVS Pharmacy	RGarcia-CVS-000001 – 25
Express Scripts Inc.	RGarcia-ES-000001 – 12
HEB Pharmacy	RGarcia-HEBPharm-000001 – 25
Kelsey Pharmacy Berthelsen	RGarcia-KelseyP-000001 – 3
Kelsey Seybold Clinic	RGarcia-KSC-000001 – 2128
Texas Digestive Disease Consultants	RGarcia-TexasDDC-000001 – 42
Walgreen Company	RGarcia-WC-000001 – 79
Kennedy, Paulette	
Plaintiff Fact Sheet	
Plaintiff Fact Sheet, 06/21/2021	PKennedy-PFS-000001 – 470
Medical Records	
Plaintiff Produced Records	PKennedy-PPR-000001 – 590
Baylor Scott and White Medical Center	PKennedy-BS&WMC-000001 – 438
Dallas Cardiac Associates	PKennedy-DCA-000001 – 25
Dallas Nephrology	PKennedy-DallasNephA-000001 – 125
Kroger Pharmacy	PKennedy-KrogerPharm-000001 – 9
Lajara, Rosemarie, MD	PKennedy-RLajara-000001 – 10
Medical City Dallas	PKennedy-MCDH-000001 – 453
Northstar Diagnostic Imaging	PKennedy-NStarDI-000001 – 33
Solis Mammography	PKennedy-SolisM-000001 – 34
Southern Endocrinology and Diabetes Association	PKennedy-SEndo&DA-000001 – 33
Texas Breast Specialists	PKennedy-TBS-000001 – 168
Texas Colon and Rectal Surgeons	PKennedy-TC&RSurgeons-000001 – 128
Texas Oncology	PKennedy-TOncology-000001 – 385
Walgreen Company	PKennedy-WC-000001 – 91
Kinkela, Silvano	
Plaintiff Fact Sheet	
Plaintiff Fact Sheet, 06/11/2021	SKinkela-PFS-00001 – 641
Medical Records	
Plaintiff Produced Records	SKinkela-PPR-00001 – 430
Aaron, Jay S., MD	SKinkela-JSAaron-00001 – 85
Advance Urology Centers of New York	SKinkela-AUCNY-00001 – 33
East Virginia ENT Specialists	SKinkela-EVEN&TS-00001 – 18
Lackawana County Dermatology Associates	SKinkela-LVDA-00001 – 19

Optum Rx	SKinkela-OptumRx-00001 – 138
Pulmonary And Critical Care Specialists	SKinkela-P&CCS-00001 – 56
Sentara Leigh Hospital	SKinkela-SentaraLH-00001 – 262
Sentara Surgery Specialists	SKinkela-SSS-00001 – 749
Urology Associates of the Poconos	SKinkela-UAP-00001 – 62
Virginia Oncology Associates	SKinkela-VOA-00001 – 93
Walgreen Company	SKinkela-WC-00001 – 24
Lee, Robert	
Plaintiff Fact Sheet	
Plaintiff Fact Sheet, 12/23/20	RLee-PFS-000001-000167
Medical Records	
Plaintiff-Produced Medical Records	RLee-PPR-000001-000958
Blue Cross Blue Shield of South Carolina	RLee-BCBSSC-000001-000092
Ctrs for Medicare and Medicaid Svcs Region 4	RLee-CMMS-R4-000001-000126
Death Certificate Proof Of Authority	RLee-DCPOA-000001-000002
Family Healthcare Clinton	RLee-FH-C-000001-000404
Greenville Health System Patient Accts	RLee-GHS-BD-000001-000027
Greenville Health System Med Recs Dept	RLee-GHS-MD-000001-001985
Greenville Memorial Hosp Rad Dept	RLee-GMH-RD-000001-000017
Greenville Memorial Hospital -Billing	RLee-GMH-BD-000001-000005
Ingles Markets, Inc.	RLee-InglesM-000001-000029
Walmart Pharmacy	RLee-WMS-000001-000027
Meeks, Ronald	
Plaintiff Fact Sheet	
Plaintiff Fact Sheet, 01/15/21	RMeeks-PFS-000001-000288
Medical Records	
Plaintiff-Produced Medical Records	RMeeks-PPR-000001-006576
Central Arkansas Veterans Healthcare System Med Recs Dept	RMeeks-CAVHS-MD-000001-000011
Central Arkansas Veterans Healthcare System Path Dept	RMeeks-CAVHS-PD-000001-000002
Death Certificate Proof Of Authority	RMeeks-DCPOA-000001-000005
East Jefferson Cardiovascular Specialists Inc Med Recs Dept	RMeeks-EJCS-MD-000001-000163
East Jefferson General Hosp Path Dept	RMeeks-EastJGH-PD-000001-000001
East Jefferson General Hosp Med Recs Dept	RMeeks-EJGH-000751-002405
East Jefferson General Hosp Patient Accts	RMeeks-EastJGH-BD-000001-000027
East Jefferson General Hosp Rad Dept	RMeeks-EastJGH-RD-000001-000001
East Jefferson Internal Medicine	RMeeks-EJIM-000001-000057
Med Plaza ENT Physicians	RMeeks-MPENTP-000001-000036
Nola Discount Pharmacy Pharmacy	RMeeks-NDP-000001-000027

Ochsner Med Ctr Release of Information	RMeeks-OchsnerMC-MD-000001-003194
Ochsner Med Ctr Patient Accts	RMeeks-OchsnerMC-BD-000001-000124
Ochsner Med Ctr Kenner Med Recs Dept	RMeeks-OMC-K-MD-000001-000797
Ochsner Med Ctr Kenner Patient Accts	RMeeks-OMC-K-BD-000001-000010
Ochsner Med Ctr Kenner Path Dept	RMeeks-OMC-K-PD-000001-000001
Ochsner Med Ctr Kenner Rad Dept	RMeeks-OMC-K-RD-000001-000001
Ochsner Medical Complex - NR Cert Ltr	RMeeks-OMComp-000001-000001
Smith Kenneth B MD	RMeeks-KBSmith-000001-000175
Southeast Louisiana Veterans HealthCare System Rad Dept	RMeeks-SLVHCS-RD-000001-000062
Southeast Louisiana Veterans Health Care System	RMeeks-SLVHCS-RD-000008-000009
Tulane Univ Hosp and Clinic Rad Dept	RMeeks-TUHC-RD-000001-000003
Tulane Univ Hosp and Clinic Med Recs Dept	RMeeks-TUHC-MD-000001-000001
Univ Med Ctr New Orleans Rad Dept	RMeeks-UMCNO-RD-000001-000002
Univ Med Ctr New Orleans Patient Accts	RMeeks-UMCNO-BD-000001-000009
Univ Med Ctr New Orleans Path Dept	RMeeks-UMCNO-PD-000001-000001
Univ Med Ctr New Orleans Med Recs Dept	RMeeks-UMCNO-MD-000001-000389
Suits, James	
Plaintiff Fact Sheet	
Fifth Amended Plaintiff Fact Sheet, 02/03/21	JSuits-PFS-001131-1224
Medical Records	
Plaintiff-Produced Medical Records	JSuits-PPR-000001-001335
Aetna US Healthcare Legal Support Svcs	JSuits-AUSH-000001-000002
John Deere - NRS	JSuits-JohnDeere-HR-000001-000001
McCaysville Internal Medicine	JSuits-McCIM-000001-000251
Mutual of Omaha Insurance Company Claims Dept	JSuits-MOIC-000001-000003
Premier Surgical Assocs Cleveland	JSuits-PremierSAC-000001-000048
Tallent Drug Store	JSuits-TDS-000001-000036
Uhlik, Allen, MD	JSuits-AUhlik-000001-000383
Weygandt, Robert	

Plaintiff Fact Sheet	
Second Amended Plaintiff Fact Sheet, 04/07/20 Plaintiff (Martha Weygandt) Fact Sheet, 03/08/21	RWeygandt-PFS-000001-000090
Depositions	
Weygandt, Martha – 2021.04.13 – Transcript	N/A
1 – 2021.03.08 Plaintiff Fact Sheet	N/A
2 – 2021.03.08 Signed Declaration of Plaintiff Fact Sheet	N/A
3 – 2014.05.22 Bankruptcy Motion for Expedited hearing on Motion to Use Cash Collateral	N/A
4 - 2019.06.17 Amended Complaint - Master Personal Injury Complaint	N/A
5 – 2020.10.21 Weygandt Short Form Complaint	N/A
6 – Weygandt Medical Records produced by Plaintiff	Various
7 – Robert Weygandt Death Certificate	RWeygandt-DCPOA-000001
8 – Weygandt Medical Records produced by Plaintiff	Various
9 – Weygandt Safeway Insurance Records	RWeygandt-Safeway-00003 – 17
10 – Weygandt Medical Record from Endocrine Associates of Dallas	RWeygandt-EAD-000055 – 60
11 – Weygandt Medical Records from Carrell Clinic	RWeygandt-CarrellC-00003 – 6
12 – Weygandt Medical Records from Dr. Potluri	RWeygandt-HHBP-MD000431 – 433
13 – Weygandt Medical Record from Endocrine Associates of Dallas	RWeygandt-EAD-000074 – 78
14 – Weygandt Medical Record from Endocrine Associates of Dallas	N/A
15 – Weygandt Medical Record from Endocrine Associates of Dallas	N/A
16 – 2020.10.30 Albertson's Defendant Fact Sheet	N/A
Medical Records	
Plaintiff-Produced Medical Records	RWeygandt-PPR-001547-001817
Abrams Royal Pharmacy II Pharmacy	RWeygandt-ARPharmII-000001-000002
Advanced Imaging Center	RWeygandt-AImagingCe-000001-83
Aetna US Healthcare Legal Support Svcs	RWeygandt-AUSH-000001-000013
Baylor Regional Med Ctr at Plano Med Recs Dept	RWeygandt-BRMCP-MD-000001-000307
Baylor Regional Med Ctr at Plano Path Dept	RWeygandt-BRMCP-PD-000001-000001
Baylor Scott and White Health Rad Dept	RWeygandt-BSW-RD-000001-000002
Baylor Scott and White Health - NRS	RWeygandt-BSW-PD-000001-000001

Baylor Scott and White Health Med Recs Dept	RWeygandt-BSW-MD-000001-000002
Baylor Scott and White Health	RWeygandt-BSW-BD-000001-17
Baylor Surgicare at Plano Patient Accts	RWeygandt-BSPlano-BD-000001-000002
Baylor Surgicare at Plano - NR Radiology Cert	RWeygandt-BSPlano-RD-000001
Blue Cross Blue Shield of Texas Claims Dept	RWeygandt-BCBST-000001-000048
Carrell Clinic - Medical	RWeygandt-CarrellC-000001-000057
Clinical Path Labs Inc	RWeygandt-CPL-000001-000004
Colon And Rectal Assocs of Texas	RWeygandt-C&RAT-000001-000027
Death Certificate Proof Of Authority	RWeygandt-DCPOA-000001-000004
DFW Smiles	RWeygandt-DFWS-000001-000018
Endocrine Assocs of Dallas	RWeygandt-EAD-000001-000342
Express Scripts Inc Recs	RWeygandt-ES-000001-000021
Fleshman James Jr MD	RWeygandt-JFleshamnJr-000001-000219
Heart Hosp Baylor Plano Med Recs Dept	RWeygandt-HHBP-MD-000001-000657
Hollabaugh, Eric, MD - Medical	RWeygandt-EHollabaugh-000001-000008
Lab Corp of America Med Recs Dept	RWeygandt-LabCorpA-MD-000002-000009
Legacy Heart Ctr Med Recs Dept	RWeygandt-LHC-MD-000001-000001
Med Ctr of Plano Med Recs Dept	RWeygandt-MCPlano-MD-000001-000122
Med Ctr of Plano Rad Dept	RWeygandt-MCPlano-RD-000001-000001
Med Ctr of Plano Path Dept	RWeygandt-MCPlano-PD-000001-000002
Med Clinic of North Texas PA	RWeygandt-MCNT-000001-000093
North Central Surgical Ctr	RWeygandt-NCSC-000001-000250
North Point Lab	RWeygandt-NPL-000001-000001
Plano Dermatology Assocs	RWeygant-PDA-000001-000003
Quest Diagnostics Irving	RWeygandt-QD-Irving-000001-000002
Safeway Inc Corporate Pharmacy Dept	RWeygandt-Safeway-000001-000017

Texas Health Presbyterian Hosp Dallas Patient Accts	RWeygandt-THPHD-BD-000001-000009
Texas Health Presbyterian Hosp Dallas Path Dept	RWeygandt-THPHD-PD-000001-000001
Texas Health Presbyterian Hosp Dallas Rad Dept	RWeygandt-THPHD-RD-000001-000001
Texas Oncology Pharmacy Sammons	RWeygandt-TOPS-000001-000002
Texas Oncology Plano Prestonwood Med Recs Dept	RWeygandt-TO-PP-MD-000001-000391
TMI Sports Medicine and Orthopedic Surgery - NR Cert	RWeygandt-TMISMOS-000001-000001
Verity Cancer Center	RWeygandt-VCC-000001-56
VerityPET CT	RWeygandt-VPET-CT-000001-000065
Verity PET CT Rad Dept	RWeygandt-VPET-CT-RD-000001-000087
Walgreen Company	RWeygandt-WC-000001-000006
DIOVAN NDA DOCUMENTS	
20818 Diovan Pharmacology Review Part 1 (fda.gov)	N/A
20818 Diovan Pharmacology Review Part 2 (fda.gov)	N/A
POST-MARKETING PERIODIC SAFETY REPORTS	
ANDA 077530 **Valsartan Tablets 40 mg, 80 mg, 160 mg, 320 mg**	
Teva Pharmaceuticals, 01 April 2015 – 30 June 2015	N/A
Teva Pharmaceuticals, 04 January 2016 – 03 April 2016	N/A
Teva Pharmaceuticals, 04 April 2016 – 03 July 2016	N/A
Teva Pharmaceuticals, 04 July 2016 – 03 October 2016	N/A
Teva Pharmaceuticals, 04 October 2016 – 03 January 2017	N/A
Teva Pharmaceuticals, 01 January 2017 – 31 March 2017	N/A
Teva Pharmaceuticals, 01 April 2017 – 30 June 2017	N/A
Teva Pharmaceuticals, 01 July 2017 – 30 September 2017	N/A
Teva Pharmaceuticals, 01 October 2017 – 31 December 2017	N/A
Teva Pharmaceuticals, 01 January 2018 – 31 March 2018	N/A
Teva Pharmaceuticals, 01 April 2018 – 30 June 2018	N/A
Teva Pharmaceuticals, 01 July 2018 – 30 September 2018	N/A
Teva, 01 October 2017 – 31 December 2018	N/A
ANDA 090642 **Valsartan Tablets 40 mg, 80 mg, 160 mg, 320 mg**	
Watson Laboratories, 05 January 2015 – 04 April 2015	N/A
Watson Laboratories, 05 April 2015 – 04 July 2015	N/A
Watson Laboratories, 05 July 2015 – 04 October 2015	N/A
Watson Laboratories, 05 October 2015 – 04 January 2016	N/A
Watson Laboratories, 05 January 2016 – 04 April 2016	N/A

Watson Laboratories, 05 April 2016 – 04 July 2016	N/A
Watson Laboratories, 05 July 2016 – 04 October 2016	N/A
Teva Pharmaceuticals, 05 October 2016 – 04 January 2017	N/A
Teva Pharmaceuticals, 05 January 2017 – 04 April 2017	N/A
Teva Pharmaceuticals, 05 April 2017 – 04 July 2017	N/A
Teva Pharmaceuticals, 05 July 2017 – 04 October 2017	N/A
Teva, 01 January 2018 – 31 December 2018	N/A
ANDA 091235 **Amlodipine and Valsartan Tablets 5/160 mg, 10/160 mg, 5/320 mg, 10/320 mg**	
Teva Pharmaceuticals, 01 June 2015 – 31 August 2015	N/A
Teva Pharmaceuticals, 01 September 2015 – 30 November 2015	N/A
Teva Pharmaceuticals, 01 December 2015 – 29 February 2016	N/A
Teva Pharmaceuticals, 01 March 2016 – 31 May 2016	N/A
Teva Pharmaceuticals, 01 June 2016 – 31 August 2016	N/A
Teva Pharmaceuticals, 01 September 2016 – 30 November 2016	N/A
Teva Pharmaceuticals, 01 December 2016 – 28 February 2017	N/A
Teva Pharmaceuticals, 01 March 2017 – 31 May 2017	N/A
Teva Pharmaceuticals, 01 December 2017 – 28 February 2018	N/A
Teva, 01 March 2018 – 28 February 2019	N/A
ANDA 091519 **Valsartan and Hydrochlorothiazide Tablets 80/12.5 mg, 160/12.5 mg, 160/25 mg, 320/12.5 mg, 320/25 mg**	
Watson Laboratories, 21 March 2013 – 20 June 2013	N/A
Watson Laboratories, 21 June 2013 – 20 September 2013	N/A
Watson Laboratories, 21 September 2013 – 20 December 2013	N/A
Watson Laboratories, 21 December 2013 – 20 March 2014	N/A
Watson Laboratories, 21 March 2014 – 20 June 2014	N/A
Watson Laboratories, 21 June 2014 – 20 September 2014	N/A
Watson Laboratories, 21 September 2014 – 20 December 2014	N/A
Watson Laboratories, 21 December 2014 – 20 March 2015	N/A
Watson Laboratories, 21 March 2015 – 20 June 2015	N/A
Watson Laboratories, 21 June 2015 – 20 September 2015	N/A
Watson Laboratories, 21 September 2015 – 20 December 2015	N/A

Watson Laboratories, 21 December 2015 – 20 March 2016	N/A
Teva Pharmaceuticals, 21 March 2016 – 20 March 2017	N/A
Teva Pharmaceuticals, 21 March 2017 – 20 March 2018	N/A
ANDA 200435 **Amlodipine, Valsartan and Hydrochlorothiazide Tablets 5/16012.5 mg, 10/160/12.5 mg, 5/160/25 mg, 10/160/25 mg, 10/320/25 mg**	
Teva Pharmaceuticals, 01 December 2014 – 28 February 2015	N/A
Teva Pharmaceuticals, 01 March 2015 – 31 May 2015	N/A
Teva Pharmaceuticals, 01 June 2015 – 31 August 2015	N/A
Teva Pharmaceuticals, 01 September 2015 – 30 November 2015	N/A
Teva Pharmaceuticals, 01 December 2015 – 29 February 2016	N/A
Teva Pharmaceuticals, 01 September 2016 – 30 November 2016	N/A
Teva Pharmaceuticals, 01 September 2017 – 31 August 2018	N/A
MISCELLANEOUS	
All Plaintiff Diagnosis & Treatment Report	N/A
FDA Laboratory Analysis of Valsartan Products with Date Ranges	N/A
All materials cited or referenced in my expert report and curriculum vitae	N/A
All materials cited by Plaintiffs' expert witnesses - Drs. Etminan, Panigrahy, Hecht, Lagana, Madigan - in their reports and exhibits	N/A
This list includes items Plaintiffs' experts relied upon. By so doing, Defendants and this expert are not waiving any arguments or objections related to admissibility.	N/A

CHODOSH

EXHIBIT C

Testimony List – Lewis A. Chodosh, M.D., Ph.D.
7/1/2017 – 6/30/2021

1. Ingham et al. v. Johnson & Johnson et al. (MO) (deposition) – 4/27/2018
2. Deisher v. Secretary of Health and Human Services (US COFC) – 6/18/2018